pH of Medicated Syrups–Does It Really Matter? – An *in-vitro* Study: Part-II

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The aim of the present in vitro study was to quantify the endogenous erosive potential of the various pediatric liquid medicaments by measuring the calcium dissolution of primary enamel after immersing it for different time intervals (1min, 10 min and 8 hours) using atomic absorption spectrometer (AAS). The eight commonly used pediatric liquid medicaments which were selected had definitive endogenous calcium dissolution potential. All the medicaments showed calcium dissolution of primary enamel at alkaline pH and near neutral pH. The calcium dissolution potential of pediatric liquid medicaments when compared with their respective pH showed no statistically significant correlation. In ***conclusion****, there was evidence of calcium dissolution from all the pediatric liquid medicaments.*

Keywords: *Erosion, Pediatric liquid medicaments, Chelating agents, pH, Calcium dissolution*
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INTRODUCTION

Erosion lesions with multi-causative etiology are signs of dental hard tissue disease that has become commonly evident in today's society.[1-9] The incidence of erosion lesions are no longer limited to any particular age group, as manifestations can be detected throughout the entire life span. Epidemiological surveys report high incidence of dental erosion lesions among pre-school children and adults of all ages, while the percentage of the incidence peaks among the teenage populations.[10-14] Causative factors may vary from extrinsic sources such as environmental or dietary habits, to intrinsic sources such as systemic disease, or could be secondary to psychosomatic disorders.[15]

Of particular concern is tooth wear caused by dietary erosion, which is seen in individuals consuming fruit juices and carbonated soft drinks, and in those patients taking certain acidic medicines regularly and long-term, where the effects of dental erosion can add to their considerable burden of ill health.[16]

Clinical evidence has shown the dentally erosive effects of aspirin,[17] vitamin preparations in chewable tablet and lozenge and anti-asthmatic drugs.[18,19] In addition, in-vitro studies have shown the demineralizing potential of iron tonics,[20] effervescent vitamin preparations,[21] mouth rinses,[22] and medicines used in the treatment of phenylketonuria[23] and renal disease.[24, 25]

In a previous part of this study,[41] we observed that there was a definitive erosion of the primary enamel surface caused by commonly used pediatric liquid medicaments. But, it has been stated that SEM analyses should be mainly used to visualize the pathology and should not be used in isolation, without any quantitative methods.[26] Hence, the aim of the present study was to quantify the calcium dissolution from primary enamel, after immersing it in the Pediatric Liquid Medicaments (PLM) for different intervals of time (1 min, 10 min, and 8 hrs.).

MATERIALS AND METHODS

The eight commonly used pediatric liquid medicaments, which were studied for their erosive potential in the previous part of this study, were selected for the present study and their endogenous pH was measured (Table 1) using pH electrode.

Estimation of calcium dissolution potential of PLM from 50mg of enamel powder [27]

Thirteen caries free and restoration free, exfoliated or extracted primary teeth were used for this study. The internal dentin support was removed using a high speed dental hand piece. The remaining enamel shell was ground to a fine

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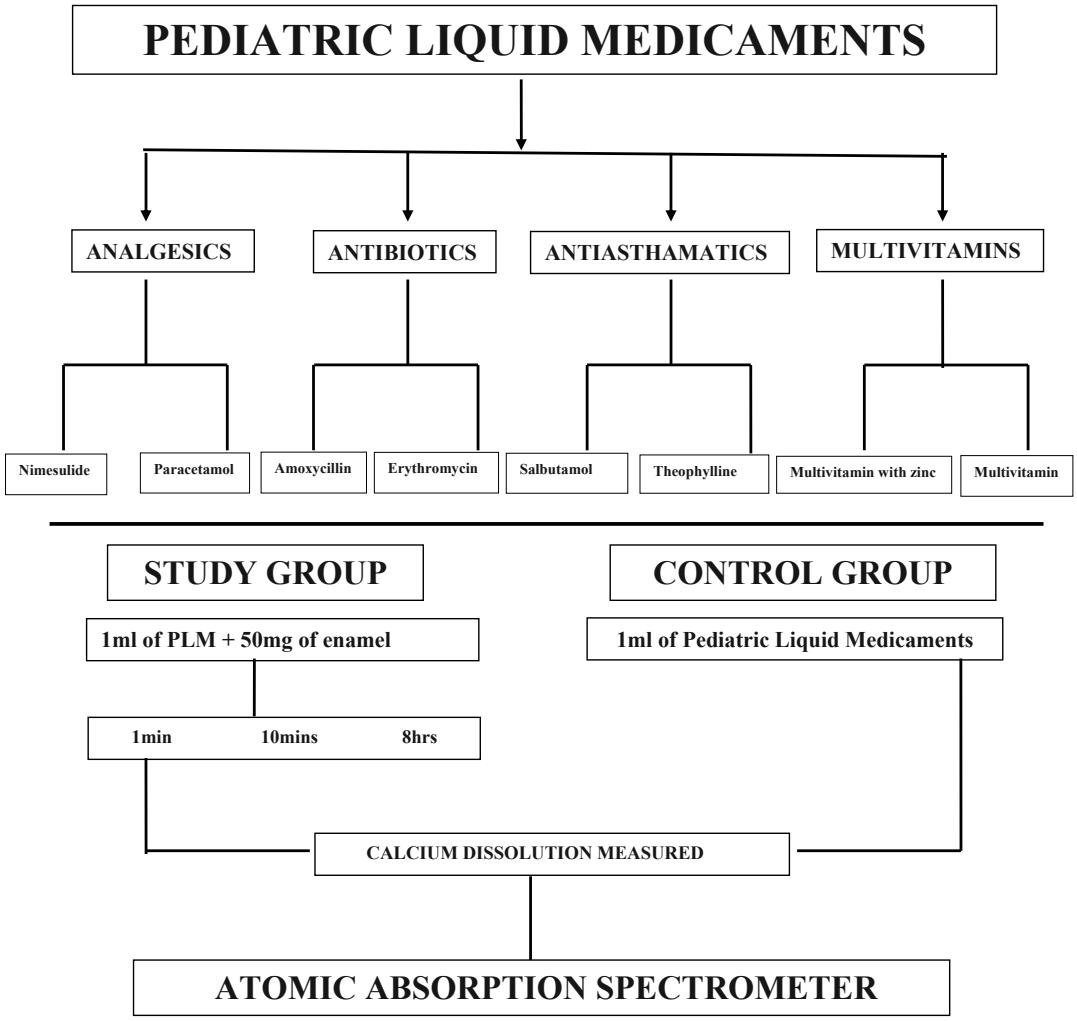
Table 1. Pediatric Liquid Medicaments used in the study and their pH

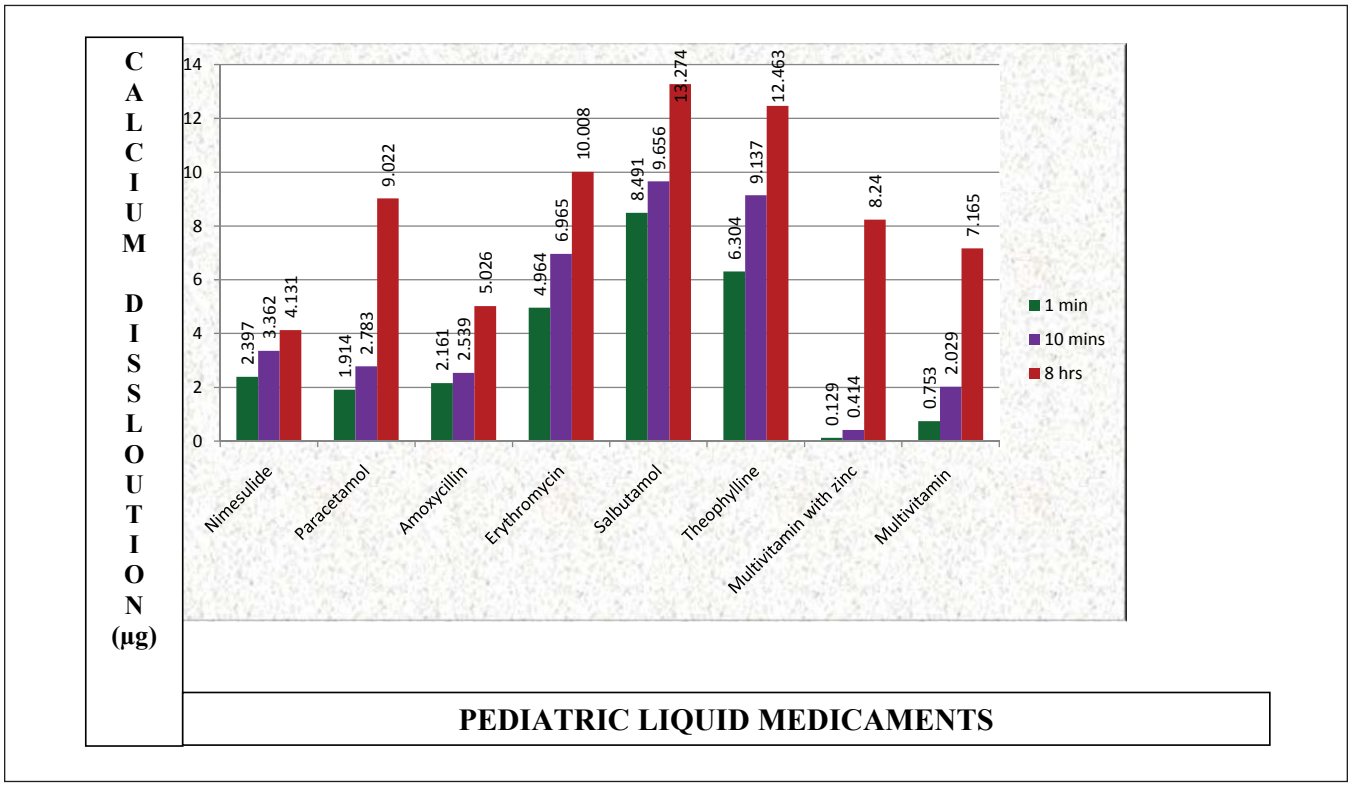
PLM	Generic Name / International Non-proprietary Name (INN)	Trade Name	Pharmaceutical company	pH of the PLM
Analgesics	Nimesulide Paracetomaol	Nise ® Crocin®	Dr.Reddy's Lab Ltd. Smithkline Beecham Asia Pvt. Ltd.	6.2 6.77
Antibiotics	Amoxycillin Erythromycin	Mox® Althrocin®	Ranbaxy Lab Ltd. Alembic Ltd.	6.62 6.73
Anti-asthmatics	Salbutamol Theophylline	Salbid® Theopid®	Eros Pharma Ltd. Cipla Ltd.	6.05 7.71
Multivitamins	Multivitamin with zinc Multivitamin	Zevit ® Vi-syneral®	Remidex Pharma Pvt. Ltd. Aviat Chemicals Pvt.Ltd	6.25 6.67

powder, by use of a mortar and pestle and pooled for these experiments.

Fifty milligram of powdered enamel (60-100 in – 1 mesh) was then mixed with 1 ml of each PLM. Duplicates were prepared excluding the powdered enamel. All mixtures were maintained at 3 different period of time (i.e. 1min, 10 min and 8 hrs). The enamel powder was removed from each sample after centrifugation for 5 min at 5000 rpm. A 0.5 ml aliquot of each supernatant was removed and placed into a porcelain crucible. The samples were dried at 100ºC for 2 hrs

Table 2. Procedure protocol for measuring the calcium dissolution from primary enamel powder





Graph 1. Calcium dissolution potential of PLM from 50 mg of primary enamel powder

in a hot air oven and ashed in a furnace at 650ºC for 18 hrs. The residue was dissolved in 0.1 ml of concentrated Hydrochloric acid and boiled gently to convert pyrophosphate back to orthophosphate. The dissolved ash was then made up to 1.0 ml with distilled water. Calcium was estimated by using atomic absorption spectrometer (Model 932plus, GBC Scientific equipment, Australia,). The amount of calcium dissolved was calculated by subtracting the calcium concentrations in the mixtures without enamel from calcium concentrations mixtures containing powdered enamel (Table 2).

STATISTICAL ANALYSIS

The data obtained was subjected to statistical analysis. Wilcoxon's Signed-Rank Sum Test & Spearman correlation coefficient was used

RESULTS

pH of the pediatric liquid medicaments

The pH ranged between 6.05 (Salbutamol) to 6.77 (Paracetamol) which were acidic, where as Theophylline had a basic pH of 7.71 (Table 1).

Calcium dissolution potential of PLM from 50mg of primary enamel surface using atomic absorption spectrometer (Tables 3 and 4)

Amount of calcium dissolution varied from 13.274µg to

Table 3. Estimation of calcium dissolution potential of PLM from 50mg of primary enamel powder using Atomic Absorption Spectrometer

PLM	Calcium present in syrups (in µg)	Calcium present in syrups at 1min (in µg)	Calcium present in syrups at 10min (in µg)	Calcium present in syrups at 8hr (in µg)	Calcium dissolution from syrups at 1min (in µg)	Calcium dissolution from syrups at 10min (in µg)	Calcium dissolution from syrups at 8hr (in µg)
Nimesulide	6.083	8.480	9.446	10.214	2.397	3.362	4.131
Paracetamol	4.768	6.682	7.551	13.790	1.914	2.783	9.022
Amoxycillin	2.346	4.505	4.885	7.372	2.161	2.539	5.026
Erythromycin	5.128	10.091	12.093	15.135	4.964	6.965	10.008
Salbutamol	2.075	10.566	11.212	15.348	8.491	9. 656	13.274
Theophylline	5.735	12.039	15.391	18.198	6.304	9. 137	12.463
Multivitamin with zinc	5.017	5.146	5.431	13.257	0.129	0.414	8.240
Multivitamin	7.018	7.771	9.047	14.183	0.753	2.029	7.165

Table 4. Statistical Analysis of Calcium Dissolution Potential of PLM

PLM	Time intervals	Paired differences: Amount of Calcium dissolution (in µg)	Paired differences: Standard deviation	Z	P
Nimesulide	1min	2.397	0.017	2.425	.038 *
	10min	3.362	0.042	3.523	.006 **
	8hr	4.131	0.032	3.489	.001 ***
Paracetamol	1min	1.914	0.004	2.123	.041 *
	10min	2.783	0.002	2.987	.009 **
	8hr	9.022	0.001	18.840	.001 ***
Amoxycillin	1min	2.161	0.001	2.247	.0402 *
	10min	2.539	0.005	2.645	.007 **
	8hr	5.026	0.008	12.560	.00 ***
Erythromycin	1min	4.964	0.008	2.456	.032 *
	10min	6.965	0.005	2.750	.0095 **
	8hr	10.008	0.005	6.321	.001 ***
Salbutamol	1min	8.491	0.003	2.321	.039 *
	10min	9.656	0.004	2.683	.006 **
	8hr	13.274	0.006	4.621	.001 ***
Theophylline	1min	6.304	0.008	2.280	.042 *
	10min	9.137	0.003	2.771	.008 **
	8hr	12.463	0.0011	5.426	.001 ***
Multivitamin with zinc	1min	0.129	0.006	2.045	.048 *
	10min	0.414	0.002	2.942	.009 **
	8hr	8.240	0.038	11.086	.001 ***
Multivitamin	1min	0.753	0.004	2.216	.043 *
	10min	2.029	0.007	2.651	.006 **
	8hr	7.165	0.003	8.742	.001 ***

*significant ** highly significant *** very highly significant

4.13µg. Highest calcium dissolution was seen with Salbutamol and the least was seen with Nimesulide. As the time of immersion in pediatric liquid medicaments increased, the amount of calcium dissolution also increased. When calcium dissolution potential of PLM was compared with their respective pH, there was no statistically significant correlation. (Table 5)

Table 5. Correlation between enamel calcium dissolution and pH of the various PLM at various intervals of time (1min, 10min & 8hr)

PLM (in µg)	pH of the PLM	ENAMEL CALCIUM DISSOLUTION		
		1min	10min	8 hr
Salbutamol	6.05	8.491	9. 6561	3.274
Nimesulide	6.2	2.397	3.362	4.131
Multivitamin with zinc	6.25	0.129	0.414	8.24
Amoxycillin	6.62	2.161	2.539	5.026
Multivitamin	6.67	0.753	2.029	7.165
Erythromycin	6.73	4.964	6.965	10.008
Paracetamol	6.77	1.914	2.783	9.022
Theophylline	7.71	6.304	9. 137	12.463
Spearman's Correlation (r)		0.163*	0.386*	0.316*

* Not statistically significant

DISCUSSION

Dental caries is the most prevalent disease of the oral cavity and may affect individuals at any stage of their lives. Nevertheless, tooth dissolution can also be caused by erosion, which is the mineral loss of dental tissue when its surface is exposed to acids or chelates, in a systematic manner and without bacterial involvement.[28]

According to Linnett and Seow, the prevalence of dental erosion has increased especially among children and adolescents.[29] The etiology has been related to the regular use of products with low endogenous pH, high acidity, and absence or low concentrations of ions including those of calcium, fluoride and phosphate in their composition. Among these products are medications that may be erosive because they possess these characteristics and which may be of particular risk when used for treatment of chronic diseases. Antihistamine containing medicines may be an example of a potentially erosive agent.[30]

Besides, the acid components found in such medications, other factors such as high frequency of ingestion (two of more times a day), bedtime consumption, high viscosity, and the collateral effect of a reduction in salivary flow may contribute to the risk of dental erosion.[29,31]

In the first part of our study, erosive effects of these pediatric liquid medicaments on the primary enamel surface were studied using SEM. We observed the different erosion patterns on primary enamel surface. As the continuation of the previous study, the present study was undertaken to quantify the calcium dissolution of primary enamel after immersing it in these PLM for various time intervals.

The pH of the each pediatric liquid medicaments used in the present study was measured as it was not specified on the data sheet. pH ranged between 6.05 (Salbutamol) to 6.77 (Paracetamol) which were acidic, whereas, Theophylline had a basic pH of 7.71.

Pediatric liquid medicaments, which were used for the study, were subjected to atomic absorption spectrometer to determine the calcium dissolution potential from primary enamel. All the medicaments studied, showed the calcium dissolution of primary enamel. Calcium dissolution was evident at alkaline pH and also acidic pH, which is very much greater than critical pH of oral cavity. These results were similar to the results obtained by McClure and Ruzicka who found decalcification in rats' enamel that was caused by citrate anions with a pH range of 5.2 to 7.2.[32]

Among the pediatric liquid medicaments included in our study pH mainly did not appear to contribute to calcium dissolution. So, probably we would relate this to chelation. Chelation means the removal of ions by "clawing" them from their surroundings even at a neutral pH.[33] Chelation is independent of pH of the medium, so that removal of such metallic ions as calcium from even a biological calcium-phosphorous system may occur at a neutral or even alkaline pH.[34] Martin *et al* proposed chelation as explanation for tooth decay, whereby the inorganic components of enamel can be removed at neutral or alkaline pH.[35]

A "chelate" is a chemical compound composed of a metal ion and a chelating agent. A chelating agent is a substance whose molecules can form several bonds to a single metal ion. In other words, a chelating agent is multi-dentate ligand.

Important examples of chelates are: the haem group of Hb, the cytochromes and EDTA. These substances form chelates with calcium ions that are both soluble and very stable. This substance can therefore dissolve highly insoluble calcium phosphates in neutral solution, thus resulting in demineralization of bone and the hard tissues of teeth.[33] Calcium dissolution, seen in our study, may be probably due to the chelating agents present in pediatric liquid medicaments which would have caused the decalcification of primary enamel surface. This finding is in confirmation with the study done by Morch et al and Onose H *et al*,[36,37] who showed that the solution of the sodium salts of various amino acids (alanine, aspartame, glutamate) and lactate, at or near neutral pH, can increase the uptake of radioactive phosphorous by enamel or loss of calcium from enamel. However, the near neutral pH decalcification may result from a chelating effect.[35]

Amount of calcium dissolution varied from 13.274µg to 4.13µg. The highest calcium dissolution was seen with Salbutamol and the least was seen with Nimesulide. In children, the lower concentration of calcium in whole saliva means that oral pH dose not have to drop as much before demineralization occurs, compared to adults. The driving force for demineralization is greater in children than in adults. However and probably more importantly, the driving force for remineralization is less in children when oral pH returns to normal. Thus, for children, the lower salivary calcium concentration means a higher critical pH and a lower driving force for remineralization compared to adults.[38] May be due to this reason maximum calcium dissolution was seen in our study at pH of 6.05.

In our study, we observed that Salbutamol had highest decalcification potential compared to other pediatric liquid medicaments in all the three intervals of time. This could be due to the fact that chelating agents added to Salbutamol are more erosive to enamel than the chelating agents present in other pediatric liquid medicaments. As the time of contact with pediatric liquid medicaments increased, the erosive potential of Salbutamol also increased. On the other hand, Nimesulide had less calcium dissolution potential than other pediatric liquid medicaments. The chelating agents added in this medicament may be less erosive or reduced levels in comparison to the other pediatric liquid medicaments.

Primary teeth are known to be less mineralized than permanent teeth and particularly as the enamel surface of primary teeth is not as mature as that of permanent teeth, therefore it is more liable to erosion. It can be speculated whether susceptibility to erosion might depend on differences in hard tissue quality, culture and/or origin of people, or perhaps even genetics and/or environmental conditions.[26]

In some children, who have to use medicines several times *per* day for long periods of time, sucrose-based medicines may contribute significantly to their caries experience.[39] 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.[40]

Since the erosion in this experiment was induced under *in vitro* conditions, it was clear that the results are not completely transferable to the *in vivo* situation. The presence of the pellicle would protect the teeth from acidic challenges. It has also been suggested that the amount and quality of saliva, in particular its buffering capacity, are important in the occurrence of dental erosion. 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. From the standpoints of both hard tissue quality and salivary conditions, primary teeth seem to be at greater risk from erosive challenges than permanent teeth[26]

Evaluation of this literature indicates that many more additional *in vivo* studies are necessary to define the role of pediatric liquid medicaments in causing erosion. Further study on composition of these pediatric liquid medicaments inclusive of various chelating agents proves mandatory from this study as this is found to function independently.

CONCLUSION

1. Statistically significant Calcium dissolution was evident from all the pediatric liquid medicaments.
2. The relationship between pH of pediatric liquid medicaments and calcium dissolution was not found to be statistically significant.

Thus, greater knowledge about the erosive effect of medicaments should direct us to evolve effective programmes to alert parents, children and pharmacist against self medication of these over-the-counter medicaments.

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REFERENCES

1. Allan DN. Dental erosion from vomiting. A case report.Br Dent J, 126: 311–2, 1969.
2. Bagarlett D, Smith B. Clinical investigations of gastro-esophageal reflux: Part 1. Dent update, 23: 205–8, 1996.
3. Zazarchik DA, Fuller SJ. Dental erosion-predominant oral lesion in gastro esophageal reflux disease. Am J Gastroenterol, 95(8 Suppl): 553–8, 2000.
4. Valena V, Young WG. Dental erosion patterns from intrinsic acid regurgitation and Vomiting. Aust Dent J, 47: 106–15, 2002.
5. Bassiouny MA, Pollack RL. Esthetic management of perimolyses with porcelain laminate veneers. J Am Dent Assoc, 115: 412–7, 1987.
6. Edwell HL, Dent CD, Sharp JG. Bulimia- induced dental erosion in a male patient. Quitessence Int, 30: 135–8,1999.
7. Eccles,JD, Jenkins WG. Dental Erosion and Diet. J Dent, 2: 153–9, 1974.
8. Harrison JL, Roeder LB. Dental Erosion caused by cola beverages. Gen Dent, 39: 23–24, 1991.
9. Meuraman JH, Vesterinen M, Wine alcohol and oral health, with special emphasis on dental erosion. Quint Int, 31: 729–33, 2000.
10. AL Dlaign YH, Shaw L, Smith AJ. Dental erosion in a group of British 14year old school children. Part III: Influence of oral hygiene practices. R Dent J, 192: 526–30, 2002.

11. AL-Majed I, Maguire A, Murray JJ. Risk factors for dental erosion in 5-6 year old and 12-14 year old boys in Saudi Arabia. Community Dent Oral Epidemiol, 30: 38–46, 2002.
12. AL –Malik MI, Holt RD, Bedi R. Erosion, caries and rampant caries in preschool children in Jeddah, Saudi Arabia .Community Dent Oral Epidemiol, 30: 16–23, 2002.
13. AL–Malik MI, Holt RD, Bedi R. Clinical and photographic assessments of erosion in 2-5 year old children in Saudi Arabia. Comm Dent Health, 18: 232–5, 2001.
14. Ganss C, Klimek J, Gieses K. Dental erosion in children and adolescents –across-sectional and longitudinal investigation using study models. Community Dent Oral Epidemiol 29: 264–71, 2001.
15. Bassiouny A, Zarrinnia. Dental erosion: a complication of Pervasive Developmental Disorder. J Clin Ped Dent, 28: 273–278, 2004.
16. Nunn JH Prevalence of dental erosion and the implications for oral health. Eur J Oral Sci, 104: 156–162, 1983.
17. Sullivan RE, Kramer WS. Iatrogenic erosion of teeth. J Dent Child, 50: 192–196, 1983.
18. Giunta JL. Dental erosion resulting from chewable vitamin C tablets. J Am Dent Ass, 107: 253–255, 1983.
19. Shaw L, Al-Dlaigan YH, Smith A. Childhood asthma and dental erosion. J Dent Child, 67: 102–106, 2000.
20. James PMC, Parfitt GJ. Local effects of certain medicaments on the teeth. Br Med J, 4848:1252–1253, 1953.
21. Meurman JH, Murtomaa H. Effect of effervescent vitamin C preparations on bovine teeth and on some clinical and salivary parameters in man. Scand J Dent Res, 94: 491–499, 1986.
22. Bhatti SA, Walsh TF, Douglas CWI. Ethanol and pH levels of proprietary mouth rinses. Comm Dent Health, 11: 71–74, 1994.
23. Kilpatrick NM, Awand H, Wilcken B, Christodoulou J. The implications of phenyketonuria on oral health. Ped Dent, 21: 433–437, 1999.
24. Ng KFS. The acid content of oral liquid and effervescent tablet formulations-implications for dental care in children. BPharm dissertation. Bradford: University of Bradford,1998.
25. Nunn JH, Ng KFS, Sharkey I, Coulthard M. The dental implications of chronic use of acidic medicines in medically compromised children. Pharm World Sci, 23: 118–119:2001.
26. Johansson AK, Sorvari R, Birkhed D, Meurman JH. Dental erosion in deciduous teeth—an *in vivo* & *in vitro* study; J Dent, (5): 333–40, 2001.
27. Erickson PK. Estimation of the Caries- related risk associated with infant formula. Ped Dent, 20(7): 395–4, 1998.
28. Ten Cate JM. What dental diseases are we facing in the new millennium? Caries Res, 35: 2–5, 2001.
29. Linnett V, Seow WK. Dental erosion in children: a literature review. Ped Dent, 23: 37–43, 2001.
30. Costal CC, Almeida ICS, Costa Filho LC. Erosive effect of antihistamine-containing syrup on primary enamel and its reduction by fluoride dentifrice. Int J Ped Dent, 16: 174–180, 2006.
31. McDonald JL, Stookey GK. Laboratory studies concerning the effect of acid-containing beverages on enamel dissolution and experimental dental caries. J Dent Res, 52: 211–216, 1973.
32. Mc Clure F.J, Ruzicka S.J. The destructive effect of citrate versus lactate ions on rats molar tooth surfaces, in vivo. J. Dent Res, 25: 1, 1946.
33. Cole AS, Eastoe JE. Biochemistry and Oral Biology. 2nd edn. Butterworth and Co (publishers) Ltd, 12–13. 1988.
34. William G. Shafer. A Textbook of Oral Pathology, 4th edn. W.B. Saunders Company, 417, 1993.
35. Martin JJ, Isenberg HD, Schatz V. Chelation, or metal binding, as a new approach to the problem of dental caries. Revista Mensual de ciencias Exactas (Madrid), 14; 311–317, 1954.
36. Onose H, Sandham HJ. pH changes during culture of human dental plaque streptococci on mitis-salivarius agar. Arch oral Biol, 21: 291–296, 1976.
37. Morch T, Punwani I, Greve E. The possible role of complex forming substances in the decalcification of the caries process. Caries Res, 5: 135–143, 1971.
38. Anderson P, Hector MP & Rampersad MA. Critical pH in resting & stimulated whole saliva in groups of children & adults. Int. J. Ped Dent, 11: 266–273, 2001.
39. Kenny JD, Somaya P. Sugar load of oral liquid medications on chronically all children. Journal scientific; 55: 43–46, 1989.
40. Marthaki E, MA Pollard, MEJ Curzon .The effect of sucrose in medicines on plaque pH. Int J Paed Dent. 5: 231–235, 1995.
41. KL Girish Babu, K Rai, AM Hedge. Pediatric liquid medicaments. Do they erode the teeth? An in vitro study-Part 1. J Clin Ped Dent, 32(3): 189–94, 2007.