Formulation and Evaluation of Amoxicillin Trihydrate Lozenges

S. Vidyadhara[1], R.L.C. Sasidhar[1], B. Deepti[2], E. Wilwin[1] and B. Sowjanyalakshmi[1]

[1]Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Chowdavaram, Guntur-19, Andhra Pradesh, India
[2]Vignan Pharmacy College, Vadlamudi, Guntur, Andhra Pradesh, India

Received: June 18, 2014; Accepted: May 06, 2015; Published (web): June 15, 2015

ABSTRACT: In the present investigation an attempt has been made to formulate medicated lozenges containing amoxicillin trihydrate. There are several amoxicillin trihydrate dosage forms in the market such as tablet, capsule, suspension and syrup. Still there is a need for more variant dosage forms which acts effectively and locally. The benefits of the present research work is to increase the retention of the dosage form in oral cavity for increased bioavailability, reduction in gastric irritation and bypassing first pass metabolism. The lozenges were prepared by heating and congealing method employing polyethylene glycol 1500 as matrix base, saccharin sodium (artificial sweetener), stevia (natural sweetener), xanthan gum (polymer), sodium carboxymethyl cellulose (polymer) as other exciepients. The prepared medicated lozenges were characterized for drug content uniformity, hardness, thickness, weight variation, friability and dissolution by standard pharmacopeal methods. The results of the evaluation tests obtained were within the limits. Accelerated stability studies were conducted as per ICH guidelines and found that there wasn't any substantial interaction among the drug, flavour and colour and the prepared formulations were found to be stable. Formulations were tested for drug exciepients interactions subjecting to IR spectral and DSC analyses. The results revealed that there was no major interactions between the drug and polymers used for the preparation of lozenges.

Key words: Amoxicillin trihydrate, lozenges, stevia, saccharin sodium, pastilles, xanthan gum.

INTRODUCTION

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility and most importantly, patient compliance.[1] The intraoral route is the most preferred due to its convenience and rapid onset of action. Intraoral dosage forms have evolved as an alternative to conventional tablets, capsules and liquid preparations.[2] Most of the intraoral dosage forms are intended to disintegrate, dissolve or release the drug in the oral cavity, where it has opportunity to be locally absorbed, in part or whole and alternatively may be swallowed and subsequently absorbed along the gastro-intestinal tract (GIT).[3]

Among the orally disintegrating forms, lozenges are solid preparations that are intended to dissolve or disintegrate slowly in the mouth. They contain one or more medicaments, usually in a flavoured, sweetened base. They can be prepared by molding (gelatin and/or fused sucrose or sorbitol base) or by compression of sugar-based tablets. Molded lozenges are sometimes referred to as pastilles while compressed lozenges are often referred to as troches. They are usually intended for treatment of local irritation or infections of the mouth or throat but may contain active ingredients intended for systemic absorption after swallowing.[4] Molded lozenges have a softer texture because they contain a high percentage of sugar or a combination of a gelatin and sugar. Lozenges have long been used to deliver topical anaesthetics and antibacterial for the relief of minor sore throat, pain and irritation.

More recently, lozenges are being used as a way to deliver drugs systemically. As the lozenge slowly dissolves in the mouth, drug is released for absorption in the mouth, either buccal or

Correspondence to: R.L.C. Sasidhar
E-mail: rlcsasidhar@gmail.com

sublingually. Lozenges are especially useful for patients who have difficulty in swallowing oral solid dosage forms.[5] This includes some paediatric and geriatric patients. Lozenges dissolve slowly in the mouth that can give maximum benefit when in prolonged contact with local tissues. Examples are Antifungal agents used for the treatment of candidacies (thrush) and sodium fluoride used for the prevention of dental caries.

Amoxicillin is a broad-spectrum, pharmacologically active beta-lactam antibiotic effective against Gram-positive and Gram-negative bacteria. It is a widely used antibiotic in human and veterinary medicine for the treatment and prevention of respiratory, gastrointestinal, urinary and skin infections due to its pharmacological and pharmacokinetic properties.

Amoxicillin trihydrate is resistant to gastric acid. Peak plasma concentration of amoxicillin trihydrate of 5 microgram/ ml has been observed in 1 to 2 hours after oral dose of 250 mg, with detectable amount present up to 8 hours. About 20% of amoxicillin trihydrate is bound to plasma protein in the circulation and plasma half lives of 1 to 1.5 hours have been reported. The half-life may be longer in neonates and elderly, in renal failure half life may be 7 to 20 hours. It is metabolised to a limited extent to penicilloic acid which is excreted in the urine. Amoxicillin trihydrate is slightly soluble in water (3430 mg/L water)[6] and in alcohol, practically insoluble in ether and fatty oils. It dissolves in dilute acids and dilute alkali hydroxides. Based on the above physicochemical and biopharmaceutical properties, amoxicillin trihydrate was selected as a drug candidate.[6]

Sweeteners are food additives that are used to improve the taste of everyday foods. Natural sweeteners are sweet-tasting compounds with some nutritional value; the major ingredient of natural sweeteners is either mono- or disaccharides. Artificial sweeteners, on the other hand, are compounds that have very little or no nutritional value. This is possible because artificial sweeteners are synthetic compounds that have high-intensity of sweetness, meaning less quantity of the compound is sufficient to achieve the same amount of sweetness. Artificial sweeteners are used in products used to limit caloric intake or prevent dental cavities. Sugar alcohols are natural compounds with varying degrees of sweetness which are often added to boost or fine tune flavors of products while increasing their sweetness. They are often used in conjuncture with natural or artificial sweeteners in order to achieve a desired degree of sweetness, taste or texture. Sugar alcohols typically provide some amount of nutrition but have other benefits such as not affecting insulin response or promoting tooth decay which makes them a popular sweetening choice.[7]

MATERIALS AND METHODS

Amoxicillin trihydrate was a gift sample from Apotex Pharma Ltd., Bangalore. Sodium Carboxy Methyl Cellulose was a gift sample from M/s. NATCO Pharma Ltd., Hyderabad. Stevia Natural Sweetner was procured from PROCARVIT Food products (India) private LTD, Coimbatore. Poly ethylene glycol 1500, hydrochloric acid, and saccharin sodium were procured from S.D Fine chem., Ltd., Mumbai. Xanthan gum was procured from High-pure fine chem., Chennai, India.

Estimation of amoxicillin trihydrate: Several methods have been reported for estimation of amoxicillin trihydrate by spectrophotometric and chromatographic techniques. In the present investigation a simple, sensitive more accurate spectrophotometric method was used for the estimation of amoxicillin trihydrate. The absorbance values of amoxicillin trihydrate were measured at a λ_{max} of 229 nm. 100 mg of amoxicillin trihydrate was accurately weighed and dissolved in few ml of 0.1N Hcl. into 100 ml volumetric flask and was further diluted to 100 ml with 0.1N HCl to get 1 mg/ml stock solution. From the standard solution, a stock solution was prepared to give a concentration of 100µg/ml in 0.1N HCl. 0.5, 1, 1.5, 2, 2.5 ml of stock solution were pipette out into a 10 ml volumetric flasks and volume was made up to the mark with 0.1 N HCl, so as to get 5, 10, 15, 20, and 25 µg/ml of standard dilutions of amoxicillin trihydrate. The absorbances of the resulting solution were measured at 229 nm using

0.1N HCl as blank. The method obeys Beer-Lambert's law in the concentration range of 5–30 µg/ml.

Saturated solubility studies. Saturated solubility studies of amoxicillin trihydrate were performed in different dissolution media. 100 mg of amoxicillin trihydrate was weighed and transferred into different conical flask. 25 ml of different dissolution media were transferred into individual conical flask and were closed appropriately. All the conical flasks were placed in the REMI incubator shaker. The shaker was allowed to operate at 50 rpm at 37 ºC ± 1 ºC for 24 hrs. Then the conical flasks were removed from the incubator shaker and the samples were filtered by using Whattmann filter paper. The clear solution obtained by filtration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 229 nm by using corresponding dissolution media as blank solutions. The absorbance values were noted. The solubility of amoxicillin in different media like 0.1N HCl (1.2 pH), pH 6.8 phosphate buffer, pH 4.6 acetate buffer and in distilled water were shown in table 1.

Manufacture of lozenges

Soft lozenges. The soft lozenges are prepared by melt and mold technique. Using general principles a base formula was designed to achieve desired weight per each lozenge in the range of 1 to 3 grams. The quantity of each ingredient needed for compounding the preparation was calculated for 20 lozenges and the required material for two extra lozenges were calculated and weighed. The PEG (Grade of 1500) was placed into a small beaker (50 ml) and heated without stirring. The remaining powders were mixed in the geometric dilution technique by using mortar and pestle. The powder mixture was passed through a 40 mesh sieve onto a glassine sheet. Once the PEG was melted, the heat was reduced and a stir bar was added with lowest spin rate. The powders were sprinkled onto the melted PEG ensuring each addition is wetted before adding additional powder. Once the powders were added to the PEG, the beaker was removed from the hotplate and colour, flavour were added and allowed to cool until it is "just cool to the back of the hand." The lozenge mold(s) were placed on an electronic balance and the weight of the mold(s) was tared out. The lozenge material was poured into each mold cavity to the calculated desired weight per lozenge using the digital balance.

Hard lozenges. The hard lozenges were prepared by heating and congealing technique. Using general principles a base formula was created to achieve desired weight per each lozenge usually of 1 to 3 grams. The quantity of each ingredient needed for compounding was calculated for 20 lozenges and the enough material for two extra lozenges were calculated and weighed. Syrup base was prepared in a copper vessel by dissolving the required amounts of sugar in water by heating and stirring for 2 hours by raising the temperature to 140 °C. Dextrose was dissolved in small quantity of water and heated it to 110 °C till dextrose dissolves completely forming as clear viscous syrup. Then the dextrose solution was poured into the sugar syrup. Heating and stirring were continued for 2 hours by raising the temperature to 160 °C till the colour changes to golden yellow. The temperature was brought down to 90 °C till a plastic mass was obtained. Drug, polymer, colour, flavour were added and mixed for 30 min. The mixture was poured into the molds. Air drying was done for 2 hours. The prepared lozenges were wrapped in aluminium foil and stored in desiccators to prevent moisture uptake. The compositions of various formulations were shown in table 3.

Evaluation of physical parameters of lozenges. Physical parameters such as weight uniformity, hardness and drug content were evaluated for prepared lozenges as per the standards of official compendium.

Drug content of lozenge formulations: 200 mg AMT equivalent lozenges was weighed and transferred into a 100 ml volumetric flask. To this small quantity of 0.1N HCl was added to dissolve. It was shaken occasionally for about 15 minutes and the volume was made up to 100 ml by adding 0.1 N HCl. The solution was filtered by using a Whattmann filter paper. The filtrate was subsequently diluted with 0.1N HCl and the absorbance was measured at 229 nm using 0.1N HCl as blank. This test was repeated

six times (N=6). The results were shown in table 3 and 4.

***In vitro* dissolution studies of lozenge formulations.** Dissolution studies were performed on lozenge formulations in a calibrated 8 station dissolution test apparatus (LABINDIA) equipped with paddles (USP apparatus II method) employing 900 ml of 0.1 N Hcl as dissolution medium. The paddles were operated at 50 rpm and temperature was maintained at 37 ºC ± 1 ºC throughout the experiment. The samples were withdrawn at 5, 10, 15, 20, 30 and 45 minutes and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment and were estimated by ELICO double beam U.V spectrophotometer at 229 nm. The dissolution studies on each formulation were conducted in triplicate. From the dissolution profiles of % drug released versus time plots various in vitro dissolution parameters like $T_{50,}$ and $DE_{30\%}$ were calculated as suggested by Khan.[8]

Taste masking evaluation. Five human volunteers were asked to hold placebo lozenge formulations prepared with two types of sweeteners in their mouth for 30 seconds (for taste evaluation) and to spit out the solution. Then the oral cavity was rinsed thoroughly with drinking water. The volunteers were asked for mouth feel.

Characterization of lozenge formulations. Based on the dissolution studies performed on all the formulations, some of the optimized lozenge formulations were selected and further investigated for DSC and FTIR analysis.

Fourier transform infrared (FT-IR) spectroscopy. Infrared spectra of drug and optimized lozenge formulations were recorded by KBr pellet method using Fourier transform infrared spectrophotometer to study any interactions between drug and exciepients. A base line correction was made using dried potassium bromide and then spectra of optimized lozenge formulations with potassium bromide were recorded. The results were shown in figure 5.

Differential scanning calorimetry (DSC). A differential scanning calorimeter (DSC 200F3, Shimadzu) was used to obtain the DSC curves of amoxicillin trihydrate and for lozenge formulations prepared by melt and mold technique method with PEG 1500 and SCMC and Xanthan gum as suspending agents representing the rate of heat uptake. About 10mg of sample was weighed in a standard open aluminium pans, were scanned from 20-450 °C, at a heating rate of 10 °C/minute while being purged with dry nitrogen. The results were shown in figure 6.

Accelerated stability studies. The formulations which showed good *in vitro* performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of lozenges and chemical stability of lozenges containing drugs. The lozenge formulations such as AM 7 and AM 15 were subjected to accelerated stability studies. The above said formulations were kept in petridishes after preparation and stored in thermostatic oven at a temperature and relative humidity of 25 ± 2 °C, 60 ± 5% RH for 6 months and 40 ± 2 °C, 75 ± 5% RH for 3 months. Then the samples of each type of formulations were evaluated for the earlier mentioned physical parameters. The lozenges were evaluated for physical parameters and drugs were analyzed for drug content uniformity by a known spectrophotometric method as described earlier. Further these lozenges were subjected to drug release studies as stated earlier.

RESULTS AND DISCUSSION

The calibration curve for the estimation of amoxicillin trihydrate in 0.1 N HCl was found to be linear and obeyed Beer's law in the concentration range of 2-25 µg/ml. Saturated solubility studies were conducted for Amoxicillin Trihydrate using different dissolution media. Amoxicillin trihydrate showed maximum solubility in 0.1 N HCl medium. The results of saturation solubility studies were shown in the Table 1. Amoxicillin trihydrate lozenges were prepared using both the suspending agents such as the xanthan gum and sodium CMC. Various sweeteners such as the sodium saccharin (artificial sweetener) and stevia (natural sweetener) were used.

Lozenges formulated using the sodium CMC as suspending agent was easily removed from the mold and more elegant in nature. Lozenges formulated using the xanthan gum as sweetener was sticky, greasy and difficult to be the mold. More amount of the xanthan gum is to be used in order to achieve the proper consistent shape and thickness. Lozenges formulated by using both the sweeteners are having the same texture. Lozenges without the suspending agents were difficult to remove from the mold and are sticky in nature. The drug content of prepared lozenges was found to be in the range of 194.6-199.8mg. Drug content estimated for all the lozenge formulations were highly uniform with less than 2.5% variation. The melt and mold technique were found to be suitable for moulding the soft lozenge formulations. All the batches of lozenges were formulated under identical conditions to minimize processing variables. The soft lozenges were prepared by using PEG 1500 in different concentrations i.e., 80 and 85%. The heating and congealing technique was found to be suitable for moulding the hard lozenge formulations. The hard lozenges were prepared by using sucrose as sweetener base up to 61.25%.

Table 1. Saturated solubility studies of amoxicillin trihydrate in different dissolution media.

Sl. No	Solvent	Amount soluble in mg/ml
1	0.1N Hcl, pH 1.2	8.98
2	Phosphate buffer, pH 6.8	1.36
3	Acetate buffer, pH 4.6	2.86
4	Distilled water	3.36

Table 2. Composition of amoxicillin trihydrate lozenges.

Formulation (mg)	Drug (mg)	PEG 1500 (mg)	Saccharin sodium (mg)	Xanthan gum (mg)	Na CMC (mg)	Stevia (mg)	Silica Gel (mg)	Flavoring agent	Total weight (in grams)
AM 1	200	1600	43	.....	.....	.....	22	2-4 drops	1.865
AM 2	200	2000	43	.....	.....	.....	22	2-4 drops	2.25
AM 3	200	2000	43	50	.....	.....	22	2-4 drops	2.30
AM 4	200	1600	43	100	.....	.....	22	2-4 drops	1.95
AM 5	200	2000	43	100	.....	.....	22	2-4 drops	2.35
AM6	200	2000	43	.....	25	.....	22	2-4 drops	2.30
AM 7	200	1600	43	.....	50	.....	22	2-4 drops	1.90
AM 8	200	2000	43	.....	50	.....	22	2-4 drops	2.35
AM 9	200	1600	.....	...	...	86	22	2-4 drops	1.90
AM 10	200	2000	.....	....	...	86	22	2-4 drops	2.30
AM 11	200	2000	.....	50	....	86	22	2-4 drops	2.35
AM 12	200	1600	.....	100	...	86	22	2-4 drops	2.00
AM 13	200	2000	.....	100	...	86	22	2-4 drops	2.40
AM 14	200	2000	....	...	25	86	22	2-4 drops	2.30
AM 15	200	1600	.....	...	50	86	22	2-4 drops	1.95
AM16	200	2000	.....	...	50	86	22	2-4 drops	2.35

Table 3. Physical parameters of amoxicillin trihydrate lozenge formulations containing saccharin sodium as sweetener.

Sl. No	Lozenge formulation	Weight uniformity (g/loz)	Hardness (kg/cm^2)	Friability loss % w/w	Drug content* (mg)
1	AM 1	1.85 ± 0.1	5.2 ± 0.1	0.58	195 ± 0.3
2	AM 2	2.25 ± 0.3	5.8 ± 0.3	0.64	196 ± 0.3
3	AM 3	2.29 ± 0.1	5.6 ± 0.3	0.68	194 ± 0.3
4	AM 4	1.95 ± 0.2	5.5 ± 0.2	0.78	197 ± 0.3
5	AM 5	2.31 ± 0.3	5.4 ± 0.1	0.54	198 ± 0.3
6	AM 6	2.13 ± 0.1	5.4 ± 0.2	0.58	193 ± 0.3
7	AM 7	1.89 ± 0.2	5.3 ± 0.1	0.62	196 ± 0.3
8	AM 8	2.26 ± 0.2	5.8 ± 0.2	0.40	194 ± 0.3

Table 4. Physical parameters of amoxicillin trihydrate lozenge formulations containing stevia as sweetener.

Sl. No	Lozenge formulation	Weight uniformity (g/loz)	Hardness (kg/cm^2)	Friability loss % w/w	Drug content* (mg)
1	AM 9	1.89 ± 0.1	5.1 ± 0.1	0.58	195 ± 0.3
2	AM 10	2.27 ± 0.3	5.8 ± 0.3	0.64	196 ± 0.3
3	AM 11	2.29 ± 0.1	5.6 ± 0.3	0.68	194 ± 0.3
4	AM 12	1.98 ± 0.2	5.5 ± 0.2	0.78	197 ± 0.3
5	AM 13	2.36 ± 0.3	5.4 ± 0.1	0.54	198 ± 0.3
6	AM 14	2.26 ± 0.1	5.4 ± 0.2	0.58	193 ± 0.3
7	AM 15	1.91 ± 0.2	5.3 ± 0.1	0.62	196 ± 0.3
8	AM 16	2.29 ± 0.2	5.8 ± 0.2	0.40	194 ± 0.3

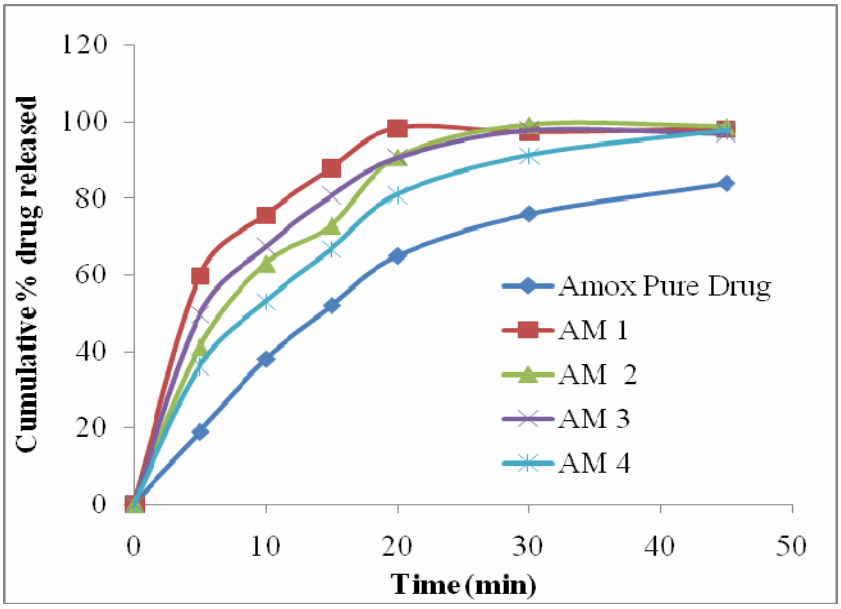

Figure 1. Drug release profiles of AMT lozenge formulations containing saccharin sodium as sweetener.

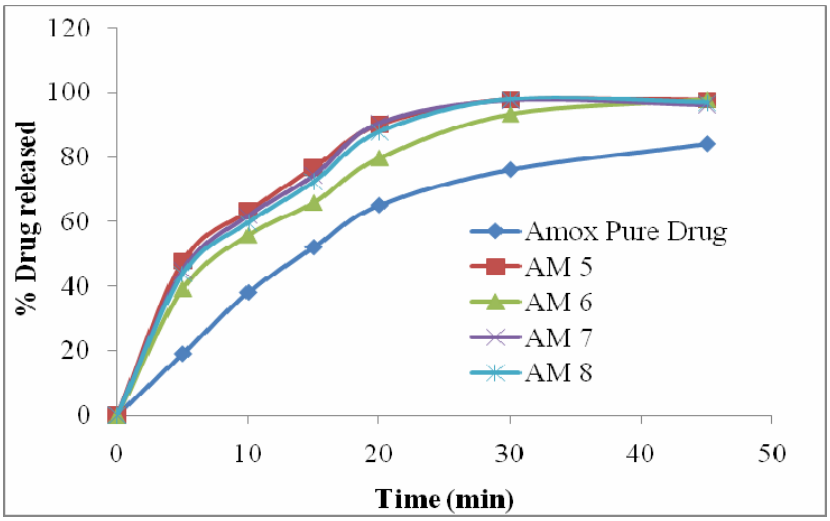

Figure 2. Drug release profiles of AMT lozenge formulations.

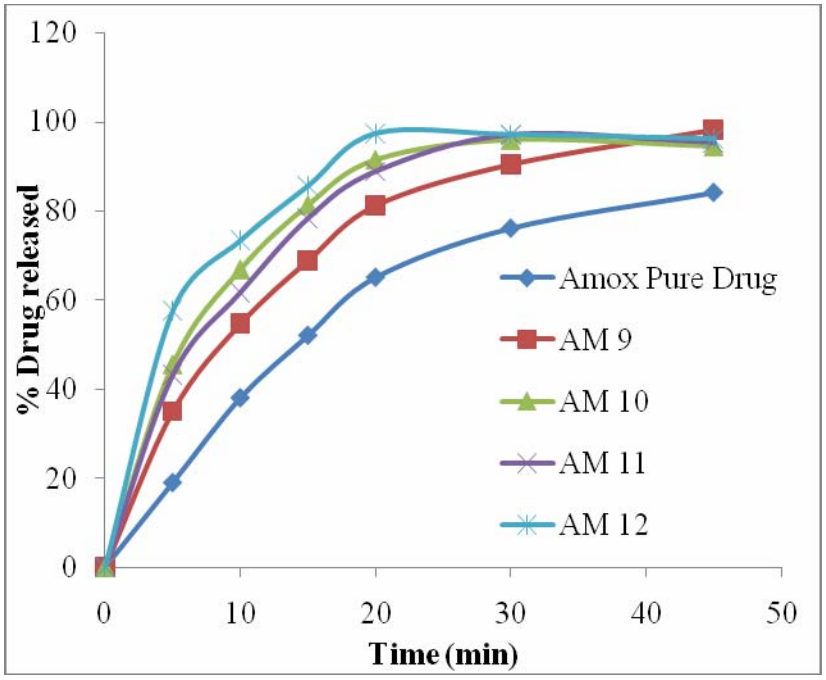

Figure 3. Drug release profiles of AMT lozenge formulations containing stevia as sweetener.

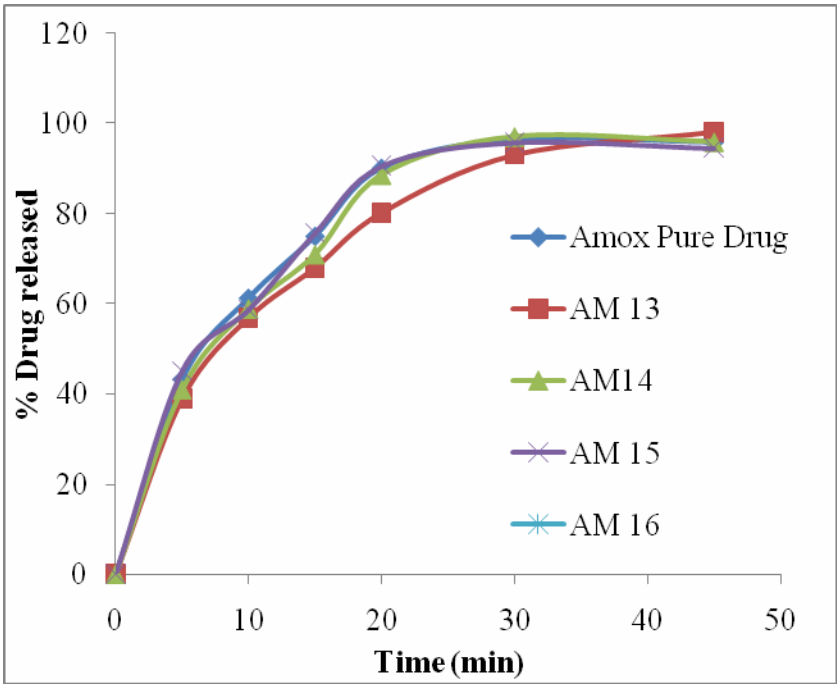

Figure 4. Drug release profiles of AMT lozenge formulations containing stevia as sweetener.

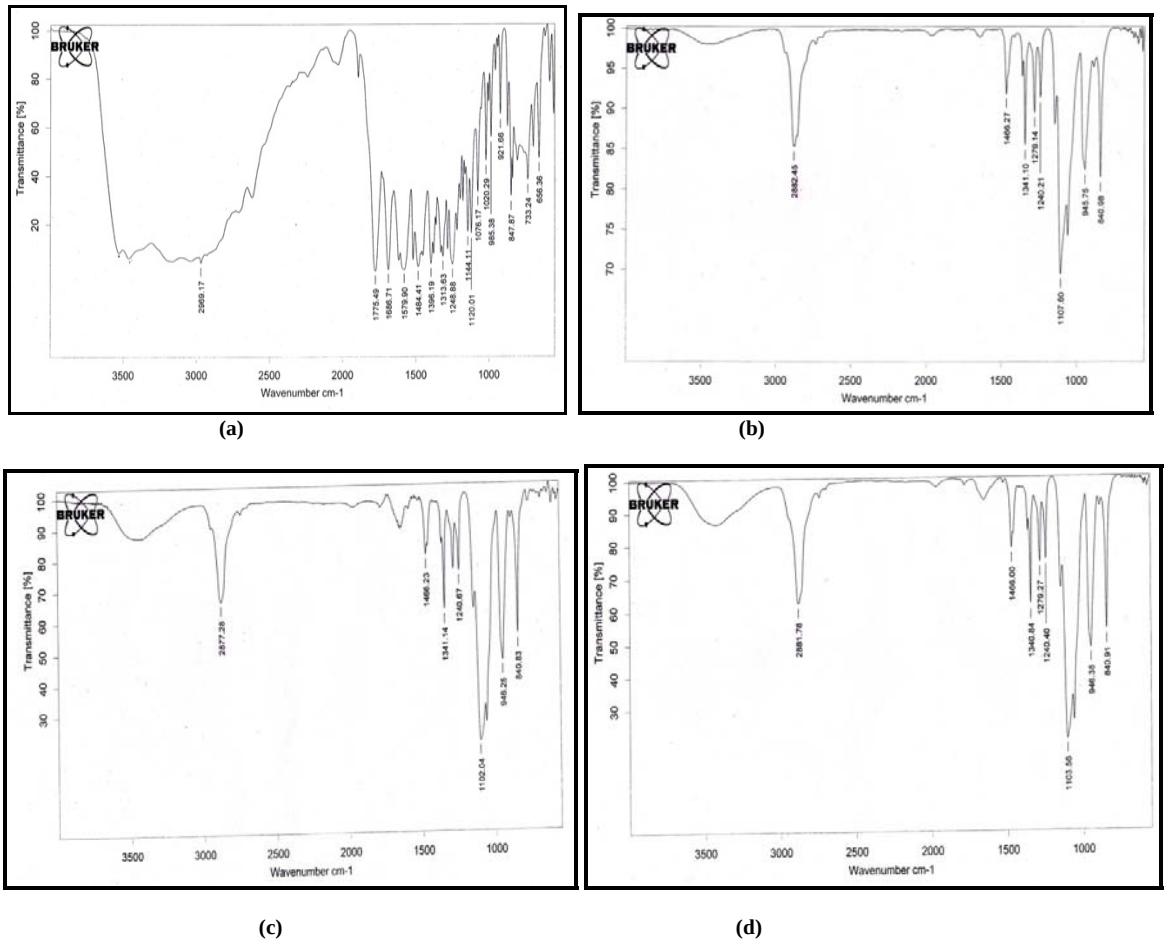

Figure 5. FT-IR spectra of (a) pure drug, (b) PEG 1500, (c) AM 7 and (d) AM 15.

All the prepared lozenge formulations were further evaluated for physical parameters. All the lozenge formulations were found to be stable and meeting I.P specified limits for weight uniformity, friability and drug content. The hardness of all the lozenge formulations was in the range of 5 - 6 kg/cm^2. Weight uniformity of all the lozenge formulations were in the range of 1.89 to 2.29 ± 0.3 g. Friability loss of the lozenge formulations were found to be negligible and were in the range of 0.58 - 0.78% w/w. The *in vitro* dissolution studies for all the lozenge formulations were found to release the drug at a faster rate than compared to pure drug. It was found that the lozenge formulations AM 7 & AM 15 with 2.5 % and 2.6 % of sodium CMC as suspending agent showed the slow drug release when compared to other formulations. The drug release of lozenge formulations in the presence of various suspending agents were in the order of sodium CMC < xanthan gum. The rate of drug release of lozenge formulations was found to be linear with first order rate constant. The R^2 values of all lozenge formulations were in the range of 0.92 to 0.99. The rate of drug release of lozenge formulations was found to be not linear with zero order rates constant. The *in vitro* dissolution studies were performed for prepared lozenge formulations in 0.1N HCl. The dissolution profiles of various formulations were shown in the figures 1-4.

It was found that the lozenge formulations prepared by melt and mold technique released the drug rapidly than the pure drug and other lozenge formulations. Dissolution parameters such as T_{50} and DE_{30} % for lozenges prepared by melt and mold techniques of AM 7 were found to be in 8 mins and 60%. Dissolution parameters such as T_{50} and DE_{30} % for lozenges prepared by melt and mold techniques of

AM 15 were found to be in 8 mins and 61.33%. Dissolution parameters such as T_{50} and DE_{30} % for the AM 17 prepared by melt and mold technique with sucrose as sweetener base was found to be 5 mins and 75%.

The optimised formulations AM7 and AM15 were subjected to accelerated stability studies and then evaluated for physical parameters, for *in vitro* drug release and further characterised by FT-IR and DSC studies. The results revealed that there was no major interaction between the drug and polymers. In FTIR studies, the groups in pure amoxicillin trihydrate and optimized formulations were having similar fundamental peaks and pattern. This indicates that there were no drug-excipient interactions in the formulations. The IR spectra of pure drug amoxicillin trihydrate, PEG 1500, AM 7, AM 15 formulations were shown in figure 5.

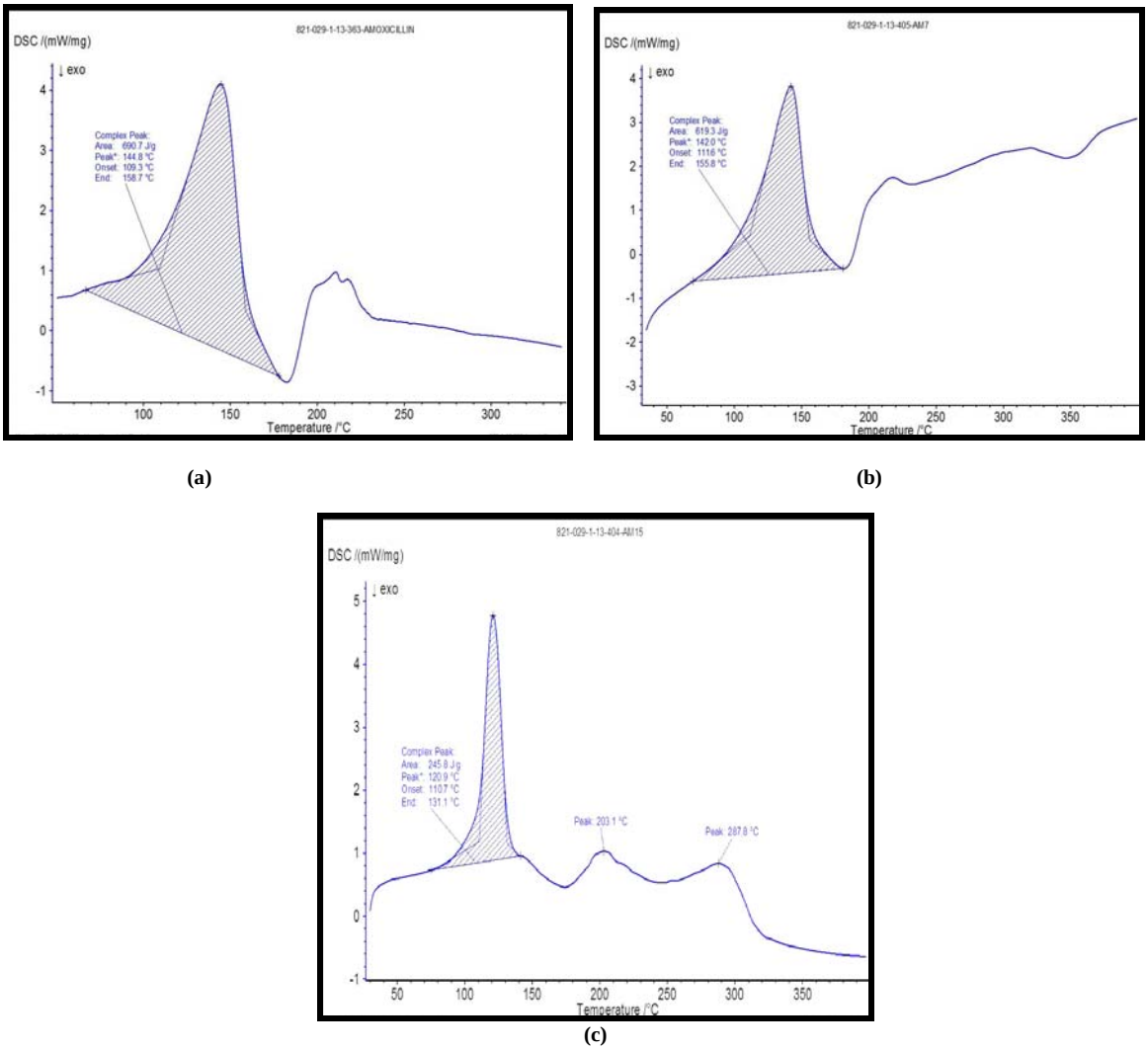

Figure 6. DSC thermograms of (a) pure drug, (b) AM 7 and (c) AM 15.

DSC analysis was performed for the Pure drug, AM 7 and AM 15 prepared by melt and mold technique. The DSC results reveal that a sharp endothermic peak for amoxicillin trihydrate was observed at 144.8 °C. An endothermic peak for amoxicillin trihydrate in AM 7 and AM 15 lozenges were observed at 142.0 °C and 120.9 °C respectively. The DSC thermograms were shown figures 6. It

indicated that there was no drug and polymer interaction. There was no significant change observed in physical parameters such as weight uniformity, friability, hardness, and drug content. Drug release from the lozenges after storage at different conditions remained unaltered and found to be quite stable.

CONCLUSION

The present study showed that it is possible to formulate the amoxicillin trihydrate as lozenges. Of all the soft lozenge formulations, the formulations AM 7 and AM 15 containing 1600 mg of PEG 1500 and 50 mg of Na CMC showed the slow release of the drug i.e. up to 45 minutes. The formulations containing stevia as sweetener are also stable after storage. Hence the natural sweeteners such as Stevia can be considered as an alternative replacement for the artificial sweeteners in the preparation of lozenges.

ACKNOWLEDGEMENTS

The authors express their gratitude to Apotex Pharma Ltd., Bangalore, NATCO Pharma Ltd., Hyderabad and PROCARVIT Food products (India) private Ltd., Coimbatore for providing the gift samples. The authors are thankful to the management of Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur for providing the facilities to carry out the research work.

REFERENCES

1. Adel, M., Semreen, and Qato, M.K. 2005. Fast dissolving dosage forms-technique. *Pharm. Tech.* **25**, 68-75.
2. Abdelbary, G., Eouani, C., Prinderre, P., Joachim, J., Reynier, J. and Piccerelle, P. 2005. Determination of the *in vitro* disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. *Int. J. Pharm*. **292**, 29-41.
3. Pfister, W. and Ghosh, T. 2005. Intraoral delivery systems: An overview, current status and future trends. Florida: CRC Press, Taylor & Francis, pp. 1-34.
4. U.S. Pharmacopeia 30-National Formulary 25. 2007. Rockville MD: *U.S. Pharmacopeial Convention Inc*. 624.
5. Kini, R., Rathnanand, M. and Kamath, D. 2011. Investigating the suitability of isomalt and liquid glucose as sugar substitute in the formulation of Salbutamol sufate hard candy lozenge. *J. Chem. Pharm. Res*. **3**, 69-75.
6. Korolkovas, A. 1998. Essentials of Medicinal Chemistry, 2nd ed., New YorkWiley-Inter Science. p. 1216.
7. Phaemachud, T. and Tuntarawongsa, S. 2010. Clotrimazol soft lozenges fabricated with melting and mold technique. *Res. J. Pharm. Biol. Chem. Sci*. **4**, 579-586.
8. Khan, K.A. 1975. The Concept of Dissolution Efficiency. *J. Pharm. Pharmacol*. **27**, 48-49.