Available on line www.jocpr.com

Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2011, 3(4):69-75

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Investigating the suitability of Isomalt and liquid glucose as sugar substitute in the formulation of Salbutamol sulfate hard candy lozenges

Rajesh Kini, Mahalaxmi Rathnanand*, Deepak Kamath

Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal University, Madhav Nagar, Manipal, Karnataka

ABSTRACT

The present investigation aims to design, prepare and evaluate the medicated hard candy lozenges of Salbutamol sulphate for paediatric, geriatric and Dysphagic patients and to investigate the suitability of Isomalt and/or liquid glucose as the sugar substitute in the prepared lozenges. The candy based lozenges were prepared by heating and congealing method in a candy based industry on request with sugar base, glycerine, citric acid artificial flavours and colours and other essential excipients. The prepared medicated lozenges were characterized for drug content uniformity, hardness, thickness, weight variation, friability, moisture content, in vitro disintegration and dissolution by pharmaceutical standard methods. Accelerated stability study conducted as per ICH guidelines (zone IV) at 45°C and 75% relative humidity over a period of seven weeks found that there wasn't any substantial interaction between the drugs, flavor and color and the prepared formulations were stable.

Keywords: Isomalt, MCI lavine buffer, hard candy lozenge, liquid glucose, moisture content analysis.

INTRODUCTION

Lozenges are the flavoured medicated dosage forms intended to be sucked and held in the mouth or pharynx containing one or more medicaments usually in the sweetened base [1,2,3]. Lozenges are intended to relieve oropharyngeal symptoms, which are commonly caused by local infections and also for systemic effect provided the drug is well absorbed through the buccal linings or when it is swallowed [4].

Salbutamol sulfate (SS), a *BCS class I* drug, is a strong β-2 agonist presently formulated as Intravenous injection; tablet and liquid orals [5].The present work has been fabricated to formulate a slow dissolving, pleasantly flavoured lozenges with a low caloric sugar substitute, Isomalt, to produce a tooth friendly dosage form.

Salbutamol is a sympathomimetics amine which is used as a bronchodilator in the treatment of reversible bronchospasm [6]. Presently, the different formulations are available for Salbutamol sulphate like IV injection, liquid inhalers, tablets and liquid orals. The tendency of Salbutamol sulphate to develop tremors in pediatric patients with a small increase in the dose has lead to the formulation problems with the oral drug delivery. However in the present study an attempt was made to develop Salbutamol sulfate hard candy lozenges to rectify the possible incompliance associated with the drug.

EXPERIMENTAL SECTION

Salbutamol Sulfate was a gift sample from Themis laboratories,Mumbai. Iso-malt (Plannit) was obtained from S.B.S Sugar free agency, Mumbai. All other chemicals and solvents were of analytical reagent grade and distilled water was used throughout the study.

Isomalt as the tooth friendly sugar substitute [7]
Isomalt does not promote dental caries because oral bacteria cannot readily convert it into decay causing acids. Therefore, the acidic conditions that lead to tooth demineralization do not develop after consuming isomalt, as occurs after eating sugar and other fermentable carbohydrates. Furthermore it's proven that the isomalt cannot be converted by oral bacteria into polyglucan, the substance from which dental plaque is synthesized.

Preparation of hard candy lozenges
Medicated boiled hard candy lozenges were prepared in a local candy industry on request. The candy based lozenges were prepared by heating and congealing method [8] in a candy based industry on request using Isomalt alone or in combination with liquid glucose as base, glycerine, citric acid artificial flavours and colours and other essential excipients.

Preparation of Glycerine mixture of drug flavour and colour solution
The glycerine mixture used in the formulation should be less than 10% of total weight of the lozenges base. About 2 ml of glycerine was taken in a 10 ml measuring cylinder in triplicate. To this added accurately weighed quantity of drug, colour and liquid flavour. This mixture was then sonicated until all the solid contents were dissolved in the glycerine mix. This glycerine mix was stored at 37^0C water bath until it is incorporated in to the final preparation.

Preparation of hard candy lozenges
Isomalt solution (70%w/v) in water was taken in a steel pan and was heated to 120^oC on a liquid paraffin bath under continuous stirring. The calculated amount of corn syrup (24DE) was added to the boiling mixture. Stirring was continued, raising the temperature to 150^oC until the mixture turned highly viscous, which was then allowed to cool to attain a temperature of 110^oC. Specified quantity of Glycerin (Table 1 and 2) containing the drug, color and flavor was added to

the above mixture under continuous stirring. The molten candy mass was then poured over a lubricated mould and was allowed to cool to room temperature.

Table 1: Composition of Hard candy lozenges containing Isomalt and liquid glucose

Ingredients	FC1	FC2	FC3	FC4
Salbutamol Sulfate (mg)	4	4	4	4
70%w/v Isomalt solution (mg)	2730	2730	2730	2730
Corn Syrup (mg)	1130	1130	1130	1130
Glycerin (ml)	0.3	0.3	0.3	0.3
Aspartame (mg)	10	10	10	10
Citric acid (mg)	5	10	15	20
Artificial liquid flavors (ml)	0.15	0.15	0.15	0.15
Color (mg)	0.5	0.5	0.5	0.5
Arachis oil	q.s	q.s	q.s	q.s

Table 2: Composition of Hard candy lozenges containing Isomalt alone

Ingredients	FC5	FC6	FC7	FC8
Salbutamol Sulfate (mg)	4	4	4	4
85%w/v Isomalt solution (mg)	3500	3500	3500	3500
Glycerin (ml)	0.3	0.3	0.3	0.3
Aspartame (mg)	10	10	10	10
Citric acid (mg)	5	10	15	20
Artificial liquid flavors (ml)	0.15	0.15	0.15	0.15
Color (mg)	0.5	0.5	0.5	0.5
Arachis oil	q.s	q.s	q.s	q.s

Characterisation of prepared tablet lozenges

The prepared formulations were evaluated for drug content uniformity, tablet hardness, thickness and diameter, weight variation, friability and *in vitro* disintegration by pharmaceutical standard methods.

Diameter

The thickness and diameter of lozenges were determined using vernier callipers. Three lozenges from each batch were used and average values were calculated.

Weight variation

The weight variation was conducted by weighing 20 lozenges individually and calculating the average weight and comparing the individual lozenges weight to the average value.

Drug content

Three lozenges from each batch were selected and weighed individually and crushed in a mortar. Drug was extracted with 100 ml of distilled water. The drug content was determined spectrophotometrically at 276 nm with blank lozenge extract as the reference.

Hardness

The hardness of the lozenges was determined by using Monsanto Hardness tester, where the force required to break the lozenges was noted.

Friability

The friability of the lozenges was determined using Roche Friabilator. Weighed lozenges were placed in the friabilator and operated for 4 min at 25 rpm. The tablets were then made free from dust and reweighed. The percentage friability was calculated.

Moisture content analysis

Moisture content in the final candy is determined by using Helium moisture balance apparatus. The sample was weighed and crushed in a mortar from this one gram of the sample was weighed and the moisture content is determined by the moisture balance apparatus.

Mouth dissolving time test

The time taken by the candy to dissolve completely was determined by the USP Disintegration apparatus, where hard boiled candy lozenges were placed in each tube of the apparatus and time taken for the lozenges to dissolve completely was noted by using MCIlavine buffer of pH 6.4 at 37^{o}C.

***In-vitro* drug dissolution studies**

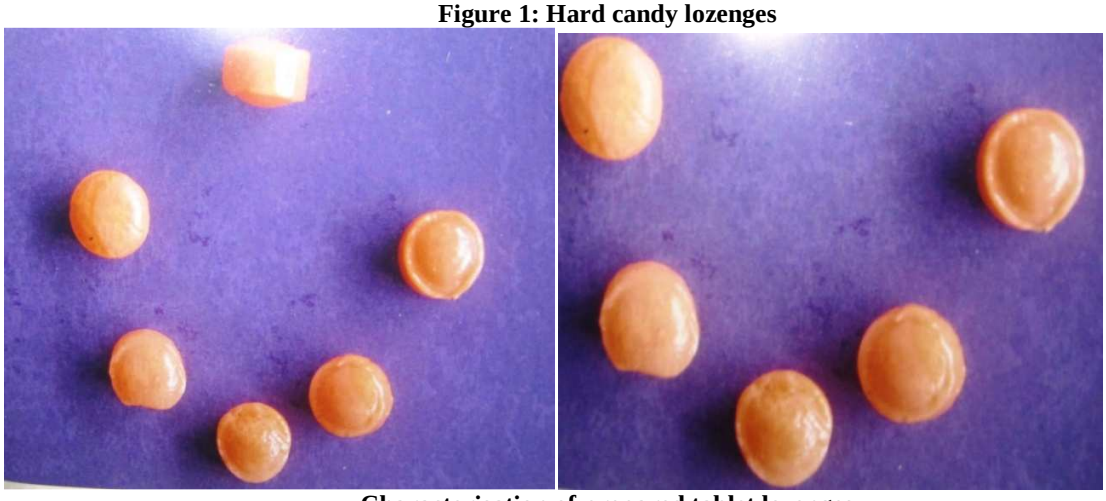
The rate of dissolution possibly is related to the efficacy of the tablet lozenge. Dissolution study was carried out in 800 ml of MCIlavine buffer pH 6.4 by USP II paddle method at 150 rpm. Samples were withdrawn at 5 min interval and replaced immediately with an equal volume of fresh buffer and were analyzed spectrophotometrically at 276 nm.

Stability studies

The stability studies were performed to assess physical as well as the chemical stability of the drug, which may possibly affect the organoleptic properties of the lozenges.

Accelerated stability study was conducted as per ICH guidelines (zone IV) at 45°C and 75% relative humidity over a period of seven weeks. Sufficient number of optimized formulations were packed in amber coloured screw capped bottles and kept in incubator maintained at 37°C. Samples were taken at intervals of 15 days to estimate the drug content and to evaluate organoleptic properties.

Figure 1: Hard candy lozenges



Characterisation of prepared tablet lozenges

RESULTS AND DISCUSSION

The prepared medicated hard candy lozenges were as shown in Figure 1.

All formulated lozenges were spherical in shape having >20Kg/cm^{2}hardness, with negligible variation in diameter (≈1 cm). Drug content uniformity, friability and mouth dissolving time was found to be within the pharmacopoeial limits as given in Table 3.

Table 3: Physicochemical characterization of lozenges

Batches	Hardness (kg/cm^2)	Weight variation (%)	Mouth dissolving time (mins)	Friability (%)	Drug content (%)	Diameter (cm)
FC1	>20	2.02 ± 0.25	31 ± 3	0.79 ± 0.3	98.39 ± 0.59	1.2±0.02
FC2	>20	2.36 ± 0.60	32 ± 1	0.77 ± 0.3	98.02 ± 0.72	1.1±0.05
FC3	>20	2.50 ± 0.50	32 ± 1	0.76 ± 0.2	97.54 ± 0.51	1.2±0.02
FC4	>20	2.51 ± 0.60	36 ± 4	0.80 ± 0.2	98.36 ± 0.24	1.1±-0.06
FC5	>20	2.30 ± 0.22	38 ± 1	0.76 ± 0.4	99.39 ± 0.62	1.1±0.02
FC6	>20	2.22 ± 0.32	36 ± 3	0.78 ± 0.2	99.01 ± 0.11	1.0±0.01
FC7	>20	2.50 ± 0.66	34 ± 2	0.77 ± 0.3	98.54 ± 0.18	1.2±0.03
FC8	>20	2.70 ± 0.54	35 ± 4	0.79 ± 0.3	99.36 ± 0.36	1.2±0.05

Moisture content analysis

The optimum range of moisture content in the hard candy based lozenges is 0.5 - 1.5%. The percentage moisture content of all the prepared hard candy lozenges was found to be < 0.8% as shown in Table 4.

Table 4: Percentage moisture content of hard candy lozenges

Formulations	% Moisture content
FC1	0.79 ± 0.32
FC2	0.768 ± 0.35
FC3	0.76 ± 0.20
FC4	0.80 ± 0.25
FC5	0.76 ± 0.47
FC6	0.78 ± 0.24
FC7	0.77 ± 0.38
FC8	0.79 ± 0.36

In vitro drug dissolution studies

Hard candy lozenges inherently possess extended release property since the drug is supposed to release from the boiled and congealed candy base.

The formulations FC4 and FC8 showed a release of 95.12% and 96.36% respectively in 60 minutes (Fig 2 and Fig 3). The release of FC8 was found be good in comparison to other hard candy lozenges, which may be attributed to the method of preparation, wherein the drug is more uniformly distributed in the lozenge in which isomalt alone is used as the sugar substitute.

Formulations FC4, prepared with Isomalt in combination with liquid glucose showed no considerable difference in the release of the drug, which showed that the Isomalt can be successfully used as the sugar substitute in the medicated lozenges.

Also, the presence of saliva stimulating agent, citric acid in higher concentration leads to the faster dissolution of the prepared formulations.

Figure2: *In vitro* release profile of the formulations FC1to FC4 containing Isomalt and liquid glucose

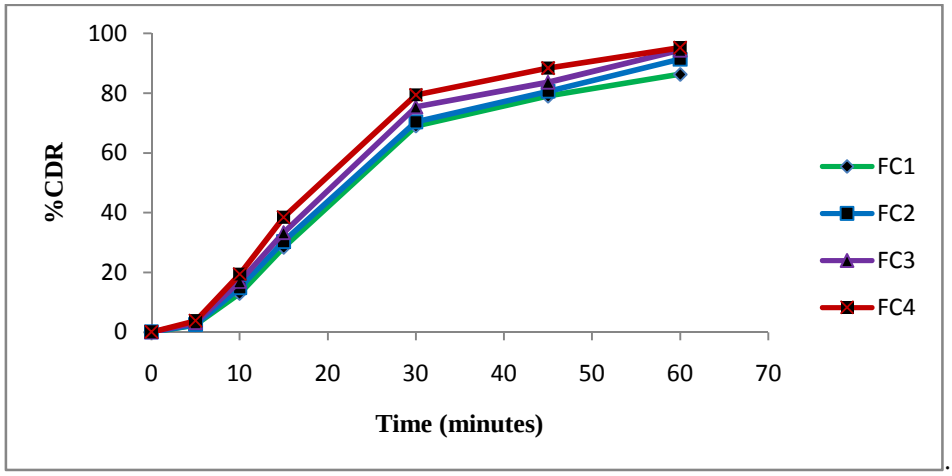
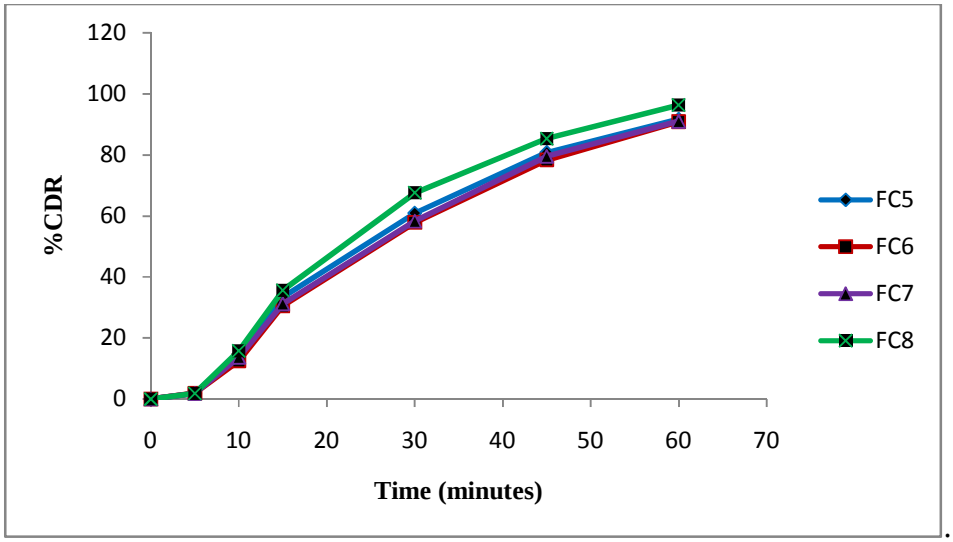


Figure 3: *In vitro* release profile of the formulations FC5to FC8 containing Isomalt alone



Stability studies

It was observed that the concentrations of drug in all the formulations were decreased a bit, however within the pharmacopoeia limits. In the evaluation of physical stability of lozenges it was found that there was a slight change in taste of all the lozenges. In colour evaluation, there observed a slight change in the intensity of colour. Hence in the stability studies carried for seven weeks it was found that there wasn't any substantial interaction between the drug, flavor and colour and the prepared formulations were stable throughout the study.

CONCLUSION

The present study was focused on the formulation and evaluation of Salbutamol sulfate lozenges by utilizing Isomalt as a vehicle which dissolve slowly in the mouth which prevail over the problem of dysphagia which is commonly associated with pediatric, geriatric, patients suffering from nausea (in cancer patients) and other patients having a problem in swallowing tablets.

Hard candy lozenges prepared from Isomalt alone and in combination with corn syrup (liquid glucose) exhibits good physical properties and showed extended drug release profile for the span of 60 minutes. The stability studies carried for seven weeks proved that the prepared lozenges were found to be stable and there wasn't any substantial interaction between the drug, colour and flavor.

From the present work, it can be concluded that the Isomalt can be successfully used as the tooth friendly sugar substitute in the formulation of medicated lozenges and owing to its low caloric value and its ability to withstand formation of plaques, it could be used safely for paediatric patient concerns. The findings from the present work could be of potential use in designing such formulations for Dysphagic patients.

REFERENCES

[1] SV Sastry, JR Nyshdham. and JA Fix, *Pharmaceutical Science and Technology Today*. **2000**, 3,138-45.
[2] J F Firriolo, *Oral Surg. Med. Oral Pathol*,**1994**, 78: 2,189-93.
[3] H Mohan.,Text book of Pathology – The oral cavity and salivary glands. 4th edn., Jaypee Brothers, Medical Publishers (P) Ltd., New Delhi; **2000**, 494-96.
[4] A Herbert, LL Lieberman, "Medicated Lozenges",Pharmaceutical dosage forms – tablet series, 2nd Edn ,Marcel Dekker Inc. New York and Basel, **1991**, I: 339-467
[5] S Dineshmohan, K Vanitha, A Ramesh, G Srikanth and S Akila, *International Journal of Research in Pharmaceutical and Biomedical Sciences*, **2010**, Vol. 1 (2), 105-108.
[6] AKM Moyeenul Huq, S U Ahmed, MQ Ahsan, *Journal of Chemical and Pharmaceutical Research*, **2011**,3(1): 14-23
[7] D Bhowmik, B Chiranjib, Krishnakanth, Pankaj and RM Chandira, *Journal of Chemical and Pharmaceutical Research*, **2009**, 1(1): 163-177
[8] K P Rao, SN Nagoba, S Zakaullah, H Zainab and S Arshiya, *Journal of Chemical and Pharmaceutical Research*, **2010**, 2(3):640-646