International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.3, No.3,pp 1375-1381, July-Sept 2011

Exploring the use of Isomalt as the tooth friendly sugar substitute in the formulation of Salbutamol sulfate compressed tablet lozenges

Rajesh Kini, Mahalaxmi Rathnanand*, Deepak Kamath

**Department Of Pharmaceutics,Manipal College Of Pharmaceutical Sciences
Manipal universityMadhav Nagar, Manipal – 576 104, Karnataka,India.**

***Corres. author:mahalaxmi.rathnanand@gmail.com,
mlrcops2002@yahoo.co.in***

Abstract: The objective of the present study was to formulate the medicated lozenges of Salbutamol sulphate for paediatric, geriatric and Dysphagic patients and to explore the use of Iso-malt as the sugar substitute in the prepared lozenges. The compressed tablet lozenges were prepared by wet granulation technique from three developed methods like, ordered mixture of drug, from the drug adsorbate of magnesium trisilicate and from the spray dried hybrid mixture of drug and mannitol, using Iso-malt as a sugar substitute, glycerine, citric acid artificial flavours and colours and other essential excipients. The prepared medicated lozenges were characterized for drug content uniformity, tablet hardness, thickness, weight variation, friability and *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: Ordered mixture, spray dried mixture, Isomalt, magnesium trisilicate adsorbate, MCI lavine buffer.

Introduction

The oral route of administration still continues to be the most preferred route due to its manifold advantages with ease of ingestion, pain avoidance, versatility and most important patient compliance, tablets, capsules liquid orals being most popular. However, their administration becomes difficult in case of dysphagia (difficulty in swallowing) with geriatric and pediatric patients and as a consequence of nausea associated with cancer chemotherapy, unavailability of water, sudden episodes of allergic attack and most importantly in mentally retarded patients[1]. Hence, when the drug is formulated in the form of lozenges could overcome all the fore mentioned incompliances.

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[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.

Materials and Methods

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[6]
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 its proven that the isomalt cannot be converted by oral bacteria into polyglucan, the substance from which dental plaque is synthesized.

Preparation of compressed tablet lozenges
Compressed tablet lozenges are prepared by developing three different methods under wet granulation technique which includes
1. Ordered mixing: Where drug in finely divided state is made to adhere to the coarser diluents particles by the application of frictional forces.
2. Drug adsorption: Involves the deposition of drug present in the solution on a solid.
3. Drug excipient hybrid mixing by spray drying: where liquid feed is rapidly transformed in to a fine powder.

Preparation of compressed tablet lozenges by the method of ordered mixing (F1-F4)
Ordered mixture was prepared by adding the sieved (80#) Salbutamol Sulfate in small parts to the weighed amount of Iso-malt and mixed thoroughly for 30 mins. Weighed amounts of other excipients (**Table 1)** were added to the prepared ordered mixture taken in a mortar and was granulated by wet granulation method using 15%w/v gelatin solution as a binding agent. The dried granules retained on sieve#44 when passed through sieve#22 together with 15% fines was mixed with weighed amounts of lubricant, glidant and spray dried flavor were compressed in a single punch machine with maximum force to obtain a compact flat faced tablet lozenges. Similarly blank lozenges were also prepared.

Preparation of compressed tablet lozenges of 10% Salbutamol sulfate adsorbate (F5-F8)
Salbutamol sulfate adsorbate (10%) was prepared by adding 1 g of drug in boiling water taken in a petri dish with constant stirring on a thermostatically controlled water bath. 10 g of activated magnesium trisilicate (obtained by vacuum drying at 100^{o}C and 720mmHg for 24 hours) was added to the above drug mixture and mixed thoroughly to obtain a homogenous dispersion. Finally the mixture was oven dried at 70^{o}C until the moisture content was less than 1.5%. The sieved free flowing powder was taken along with other excipients (**Table 2**) in a mortar and was then compressed to lozenges by wet granulation method as explained above.

Table 1: Composition of compressed tablet lozenges by the method of ordered mixing and wet granulation

Ingredients	F1	F2	F3	F4
Salbutamol Sulfate (mg)	4	4	4	4
Isomalt (mg)	1700	1700	1700	1700
Polyethylene glycol 8000 (mg)	375	350	325	300
Corn Starch (mg)	300	300	300	300
15% Gelatin Solution (mg)	75	75	75	75
Aspartame (mg)	10	10	5	25
Citric acid (mg)	5	5	5	5
Spray dried flavors(mg)	25	25	25	15
Color (mg)	0.5	0.5	0.5	0.5
Talc (mg)	0.0125	0.0125	0.0125	0.0125
Cab-o-sil (mg)	0.0250	0.0250	0.0250	0.0250

Table 2: Composition of compressed tablet lozenges of 10% Salbutamol sulfate adsorbate by the method of wet granulation

Ingredients	F5	F6	F7	F8
Salbutamol Sulfate adsorbate (10%)	400	400	400	400
Isomalt (mg)	1600	1600	1600	1600
Polyethylene glycol 8000 (mg)	275	250	225	200
Corn Starch (mg)	200	200	200	200
15% Gelatin Solution (mg)	75	75	75	75
Aspartame (mg)	10	10	5	15
Citric acid (mg)	15	50	75	5
Spray dried flavors(mg)	25	25	25	25
Color (mg)	0.5	0.5	0.5	0.5
Talc (mg)	0.0125	0.0125	0.0125	0.0125
Cab-o-sil (mg)	0.0250	0.0250	0.0250	0.0250

Table 3: Composition of compressed tablet lozenges of spray dried hybrid mixture of mannitol and salbutamol sulfate

Ingredients	F9	F10	F11	F12
Salbutamol Sulfate + Mannitol mix	40	40	40	40
Isomalt (mg)	1700	1700	1700	1700
Polyethylene glycol 8000 (mg)	375	350	325	300
Corn Starch (mg)	300	300	300	300
15% Gelatin Solution (mg)	75	75	75	75
Aspartame (mg)	10	10	5	15
Citric acid (mg)	15	50	75	5
Spray dried flavors(mg)	25	25	25	25
Color (mg)	0.5	0.5	0.5	0.5
Talc (mg)	0.0125	0.0125	0.0125	0.0125
Cab-o-sil (mg)	0.0250	0.0250	0.0250	0.0250

Preparation of compressed tablet lozenges by using spray dried hybrid mixture of mannitol and Salbutamol sulphate (F9-F12)

Spray dried hybrid mixture is prepared by separately dissolving weighed quantity of mannitol in distilled water (**Table 3),** to which 10%w/w of drug was added with stirring. This homogenous solution is then fed into mini spray drier using a pressure atomizer through rotating wheel with an atomizing air pressure of 5 kg/sq inch. The inlet temperature (140/160^{o}C), feed pump speed (2/4 ml/min), aspirator level (20/40) and concentrations of mannitol (10%/20%) used were carefully optimized.

Weighed quantity of this hybrid mixture was taken along with other excipients (Table 3) in a mortar, and was then compressed to lozenges by wet granulation method as explained above.

Characterisation of prepared tablet lozenges

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

Thickness and diameter

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

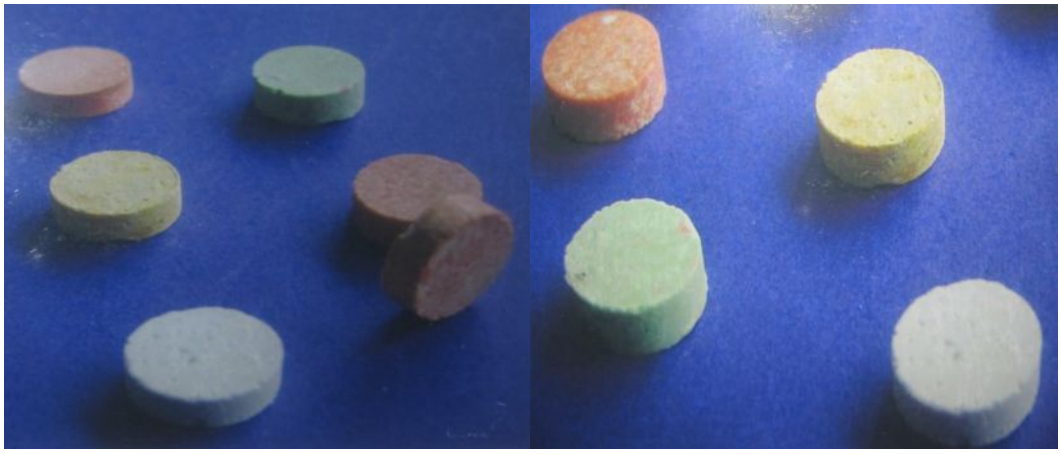
Weight variation

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.

Figure1: Compressed tablet lozenges



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.

Disintegration test

The disintegration time of lozenges were determined by USP Disintegration apparatus and disintegration time was noted in MCIlavine buffer of pH 6.4 at 37^{o}C.

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

The rate of dissolution possibly be 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 100 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 (10) 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.

Table 4: Physicochemical characterization of lozenges

Formulations	Hardness (kg/cm^3)	Weight variation (%)	Disintegration (mins)	Friability (%)	Drug content (%)	Thickness (cm)
F1	>20	4.86 ± 0.23	42 ± 2	1.08 ± 0.1	99.37 ± 0.74	1.52±0.12
F2	>20	4.32 ± 0.31	32 ± 1	0.96 ± 0.4	96.51 ± 0.34	1.44±0.11
F3	>20	4.12 ± 0.31	30 ± 6	1.02 ± 0.6	98.65 ± 0.86	1.48±0.12
F4	>20	3.60 ± 0.41	40 ± 5	0.92 ± 0.2	99.34 ± 0.14	1.51±0.23
F5	>20	3.38 ± 0.25	40 ± 5	1.08 ± 0.4	98.35 ± 0.84	1.42±0.11
F6	>20	3.39 ± 0.31	46 ± 3	0.94 ± 0.6	99.24 ± 0.65	1.51±0.10
F7	>20	4.94 ± 0.43	31 ± 4	0.80 ± 0.2	97.29 ± 0.31	1.43±0.13
F8	>20	3.62 ± 0.25	42 ± 2	0.96 ± 0.3	98.82 ± 0.54	1.56±0.14
F9	>20	4.25 ± 0.20	30 ± 6	0.86 ± 0.6	99.64 ± 0.45	1.44±0.11
F10	>20	3.29 ± 0.21	26 ± 2	0.81 ± 0.5	99.72 ± 0.54	1.48±0.10
F11	>20	2.60 ± 0.35	29 ± 1	0.84 ± 0.2	98.49 ± 0.26	1.45±0.09
F12	>20	4.89 ± 0.40	41 ± 2	0.88 ± 0.1	99.45 ± 0.63	1.51±0.12

Figure 2: *Invitro* release profile of the formulations F1to F4 prepared from Ordered mixtures

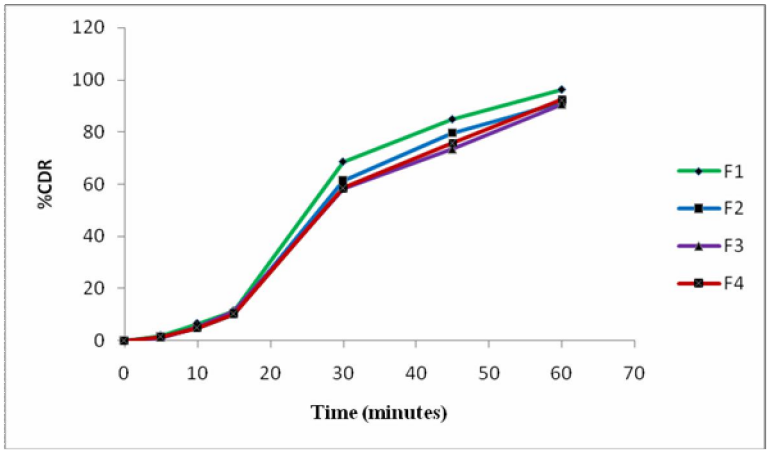


Figure 3: *Invitro* release profile of the formulations F5to F8 prepared from Drug adsorbate

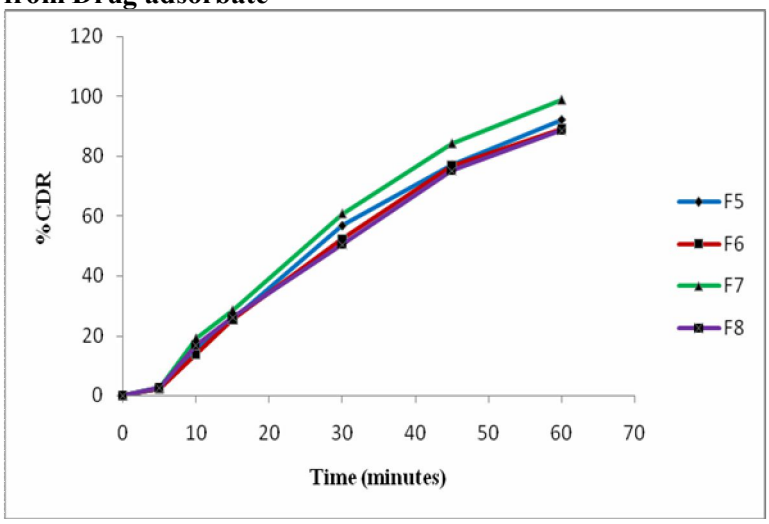


Figure 4: *Invitro* release profile of the formulations F9to F12 prepared from spray dried hybrid mixture

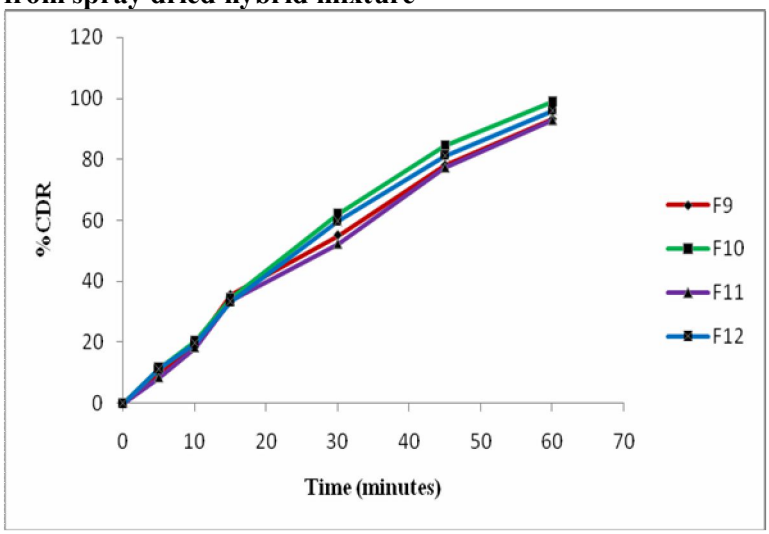
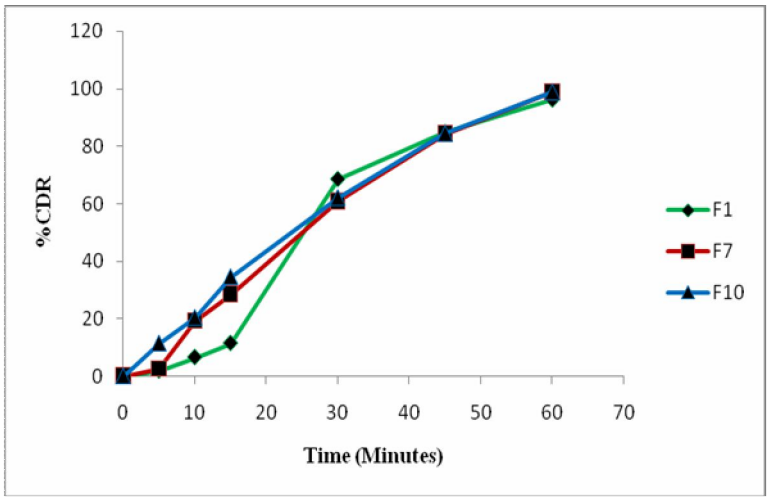


Figure 5: *In vitro* release profile of the optimised formulations F1,F7 and F10



Results and Discussion

Characterisation of prepared tablet lozenges

All formulated lozenges were spherical in shape having >20Kg/cm^{2}hardness, with negligible variation in thickness (≈1.5 cm). Drug content uniformity, friability and disintegration time was found to be within the pharmacopoeial limits as given in Table 4.

In vitro drug dissolution studies

The release profile for the formulations prepared from the ordered mixture of drug and excipient is as shown in the figure 2**.** Formulation F1 showed a release of 96.3 % in 60 minutes, which was relatively faster in comparison to the other formulations prepared from ordered mixture, which may be due to the presence of Polyethylene glycol 8000, which aid in faster disintegration of the prepared lozenges. Hence the formulation F1 can be considered as the optimised formulation prepared from ordered mixtures.

The release profile for the formulations prepared from the drug adsorbate is as shown in the figure 3. Formulation F7 showed a release of 98.9% in 60 minutes. The release from the drug adsorbate was relatively faster in comparison to that from ordered mixture. Hence the formulation F7 can be considered as the optimised formulation prepared from drug adsorbate.

The release profile for the formulations prepared from the spray dried hybrid mixture is as shown in the figure 4. Formulation F10 showed a release of 98.7% in 60 minutes. The release from the formulations prepared from spray dried hybrid mixture was relatively faster and uniform in all the prepared batches, which may be due to the uniform distribution of the drug in the hybrid mixture by spray drying method. Hence the formulation F10 can be considered as the optimised formulation prepared from spray dried hybrid mixture.

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.

All three methods of preparing compressed tablet lozenges employed achieved ideal content uniformity with optimum 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.

Hence the result indicates that isomalt owing to its low caloric value can be successfully utilized as a tooth friendly sugar substitute in the formulation of medicated lozenges. The findings from the present work could be of potential use in designing such formulations for Dysphagic patients.

References

1. Sastry S.V., Nyshdham J.R. and Fix J.A.,Recent technological advances in oral drug delivery: A

review, Pharmaceutical Science and Technology Today. 2000, 3,138-45.
2. Firriolo John F., Oral Surg. Med. Oral Pathol,1994, 78: 2,189-93.
3. Mohan H.,Text book of Pathology – The oral cavity and salivary glands. 4th edn., Jaypee Brothers, Medical Publishers (P) Ltd., New Delhi; 2000, 494-96.
4. Herbert A., Lieberman, Lachman L., "Medicated Lozenges",Pharmaceutical dosage forms – tablet series, Marcel Dekker Inc. New York and Basel, 1991; 2nd Edn. I: 339-467
5. Dineshmohan S., Vanitha K., Ramesh A., Srikanth G. and Akila S.,Formulation and Evaluation of Salbutamol Sulphate Fast Dissolving Tablet, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2010,Vol. 1 (2),105-108.
6. Featherstone J.D.B, "Effects of Isomalt sweetener on the caries process:A review",journal of Clinical Dentistry,1994,5,82-85.

*****