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RESEARCH ARTICLE

Fabrication of Palatable Medicated Chocolate of Salbutamol and Ambroxol for Pediatric Delivery

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Abstract

Chocolate as a dosage form is the most adaptable and versatile form that attractschildren of all age groups. The present research work is to design and fabricate a palatable medicated chocolate to deliver salbutamol and ambroxol for pediatric care or prescription.Preformulation studies such as DSC, FTIR, melting point and solubility were carried out to detect any incompatibility and purity of the drugs.Medicated chocolate was formulated by incorporating the drugs into the chocolate base, with desirable viscosity. Three formulations were prepared and evaluated for physical appearance, drug excipient compatibility, weight variation, thickness, drug content, *in-vitro* drug release, bloom strength, stability and release kinetics. The parameters were within official specifications for formulation F3. The *in-vitro*drug release for optimal formulations is 86.7% and 89.4% for salbutamol and ambroxol, respectively and followed zero-order kinetics and fickiantransport from the dosage form. No significant changes in the physical and chemical properties were observed during stability studies, which indicate that the formulated medicated chocolate was stable and could, ensure a good therapeutic effect withpatient compliance.The fabricated chocolate was elegant, smooth and creamy in texture and was excellent for taste masking unpleasant flavors associated with the drugs and excipients. The formulated chocolate may improve patient compliance as it can be used easily by pediatric patients with high preference.

Keywords: *Ambroxol, Chocolate delivery, Mucolytic, Bronchodilator, Salbutamol, Pediatric.*

Introduction

Respiratory tract infections are one of the most critical health problems worldwide among children and infants, where wheezing and cough are common symptoms. About 25-30% of infants and children have gone through these conditions at least once [1]. Wheezing will occur in 40% of children at three years of age and almost one-half of children at 6 years of age [2].

The recent development in the design of pediatric drug delivery is mostly concentratedon the development of oral formulations. Until recently, liquid dosage forms were widely usedfor children because of their ease and uncomplicated dosing. However, in 2008, a WHO expert forum proposed a paradigm shift towardsusing pediatric oral solids in view of stability concerns, high transportation and storage costs involved in liquid formulations [3, 4]. Chocolate is the most popular food product loved by children all over the world. It is derived from beans of the center part of the fruit of Theobroma cocoa [5].

The active ingredient theobromine in cocoa beans has a wide range of therapeutic properties like diuretic, vasodilation, muscle relaxation, anti-cancer, anti-inflammatory, anti-depressant and other beneficial effects to prevent heart diseases, improve cardiac functioning and memory. These benefits of chocolate enable it to be used in chocolate drug delivery systems. Chocolates as medicated formulations were prepared with the drug(s) incorporated into the chocolate base, which is now emerging as the novel

drug delivery system for pediatric patients [6, 7]. Salbutamol has become a vital drug in respiratory medicine for disease conditions like asthma and chronic obstructive pulmonary disease. It is one of the most commonly used medicines of choice in pediatric practice [8]. Salbutamol is generally given via a pressurized metered-dose inhaler with a large volume spacer. However, it can also be inhaled via a dry powder inhaler or nebulizer or given orally or intravenously.

Ambroxol is a secretolytic agent widely used in acute and chronic bronchopulmonary diseases associated with abnormal mucus secretion and impaired mucus transport [9]. Combinations of bronchodilators [like salbutamol] and mucolytic agents [like ambroxol] are used to treat cough in children. The patients include children of different age groups for the treatment of different conditions like bronchitis, bronchial asthma and the associated conditions like wheezing and chest congestion.

The idea of administering salbutamol and ambroxol through a chocolate delivery has definite edge over other dosage forms in quick absorption, onset of action and masking the undesirable feel and taste of the drugs for a pediatric formulation. The dosage form enables oropharynx deposition of the active molecule thus giving a simultaneous decongestant and bronchodilator effect, which chocolate delivery systems are gaining under appeal in recent times for pediatric drugs. The aim of the present research work was to design and fabricate medicated chocolates using salbutamol and ambroxol as key ingredients to be given orally to children for improved portability in pediatric drug delivery.

Materials and Methods

Materials

Salbutamol sulfate and ambroxol hydrochloride were obtained from Apex Laboratories Pvt. Ltd., Chennai, India. Cocoa powder and cocoa butter were purchased from Yarrow Chem Products, Mumbai, India. Lecithin and pharmaceutical grade sugar were purchased from Hi media Laboratories Pvt. Ltd. and Yash Pharma Sugar, Mumbai, India, respectively. All other chemicals used were of analytical grade obtained from Hi media.

Methods

Drugs and Excipients Compatibility Study

Fourier transform infrared spectroscopy [FTIR]and differential scanning colorimetry [DSC]analyses were performed for drugs, chocolate base and other excipients used in the formulations to confirm whether the drugsand excipientswere compatible[10].

Preformulation Studies

Salbutamol sulfate and ambroxol hydrochloride were subjected to preformulation studies such as solubility, melting point, partition coefficient and calibration curve toconfirm the physiochemical stability and safety of the dosage form.

Preparation of Chocolate Base

The chocolate base was prepared as per the composition specified for dark chocolate in European Commission Directive, 2000; Codex Revised Standard, 2003, as mentioned in Table 1. Chocolate designates a product containing not less than 35% of total dry cocoa solids, not less than 18% cocoa butter and not less than 14% of dry non-fat cocoa solids.

The syrup was prepared with pharmaceutical-grade sugar and water kept in the oven at 50°C for 4-5 min. Cocoa butter was kept in the oven and heated for 1 min. The prepared syrup was mixed well with cocoa powder and melted cocoa butter. Careful attention to temperature control was ensured during the process to avoid caramelization. The melted chocolate base was cooled to semisolid consistency and the flavor was added.

Formulation of Medicated Chocolates

The three formulations F1, F2 and F3 were formulated, each with a batch of 10 units as per the formula mentioned in Table 2. The chocolate base was melted in an oven at 50°C until the mass was converted to liquid. In formulation F1, the required quantity of drugs and lecithin were added to the molten base with constant stirring using a magnetic stirrer for uniform mixing. The above mixture was transferred into a polycarbonate mould and refrigerated for 15 min until solidification.

Formulation F2 was prepared with each unit containing the required quantity of drugs and

lecithin. Flavoring agent was added to the molten base to mask the odor of cocoa powder and lecithin. Formulation F3 was prepared by the addition of dicalcium phosphate as an adsorbent with the sequential addition of all the ingredients into the hot melt base [11].

Table 1: Composition of formula for the chocolate base

S. No	Ingredient	Category	Quantity
1.	Cocoa powder	Principle ingredient	1450mg
2.	Cocoa butter	Solidifying agent	500 mg
3.	Lecithin	Emulsifier	50 mg

Table 2: Composition of the various formulations of medicated chocolate of salbutamol sulfate and ambroxol hydrochloride

S. No	Ingredients	Category	Quantity[mg]		
			F1	F2	F3
1	Salbutamol sulfate	Drug	1	1	1
2	Ambroxol hydrochloride	Drug	30	30	30
3	Cocoa powder	Principle ingredient	1414	1414	1250
4	Cocoa butter	Solidifying agent	500	500	500
5	Lecithin	Emulsifier	50	50	50
6	Pharmaceutical grade sugar	Sweetening agent	1000	1000	1000
7	Dicalcium phosphate	Adsorbent	-	-	250
8	Vanilla flavor	Flavoring agent	-	15	15

Evaluation of Medicated Chocolates

Determination of Viscosity of the Chocolate Base

The viscosity of the chocolate base has a significant role in maintaining proper consistency. The viscosity of the prepared chocolate base was measured in centipoise [cps] by Brookfield Rotational Digital Viscometer [DV-I+] with spindle [LV1], which was rotated at 50rpm. The samples of the chocolate base were melted at 50ºC before the test [12].

Physical Observation

The surface characteristics and shape of the medicated chocolates were evaluated. Ten chocolates from each batch were weighed and checked for the absence of pitting, fat blooming, sedimentation and migration of active ingredients by physical observations.

Weight Variation

All the medicated formulations were weighed for individual and average weight. Then, the variation from average weight was calculated [13].

Thickness and Diameter

The thickness and diameter of the formulations indicate the dimensional variables related to the molding process. Both were measured by Vernier caliper. The deviation of both was calculated and the deviation of each unit from the mean diameter should not exceed ± 5%.

Drug Content

The drug content of the medicated chocolate was measured by dissolvingit in phosphate bufferpH 6.8 and subjected to sonication. The sonicated mixture was centrifuged at 2500 rpm for 15 min for separating the chocolate base. The supernatant solution was filtered to remove any chocolate traces and the amount of drug was determined using a UV-visiblespectrophotometer at 276 nm and 244nm for salbutamol sulfate and ambroxol hydrochloride respectively [14].

Determination of Moisture Content

The moisture content of the medicated chocolate was determined by retaining it inside the desiccator under reduced pressure by applying a vacuum for 24 h. Initial weight and the final weight after 24 h were noted and the moisture content was estimated using the formula.

Moisture content (%W/W) = Initial weight- Final weight /Initial weight X 100

Blooming Tests [fat bloom and sugar bloom]

Fat bloom can occur, which is greyish streaky appearances on the surface of the chocolate.

Sugar bloom is a physical defect characterized by a white, dusty and grainy

coating that appears over the surface of the chocolate, which occurs due to the recrystallization of sugar used in the chocolate base and condensation of moisture when exposed to a different temperature other than the storage temperature.

Sugar bloom was observed by exposing the medicated chocolateto different temperature cycles by keeping the sample in a hot air oven. The sample was initially exposed to 30ºC for 1 h and at 40ºC for 1 h with an intermediate shift to room temperature for 1 h. The change in surface characteristics and the formation of a whitish layer was observed [15, 16].

In-Vitro Drug Release

In-vitro dissolution study of medicated chocolates was performed in USP dissolution apparatus Type II, using phosphate bufferpH 6.8 as a dissolution medium. The baskets of the dissolution apparatus were filled with 900mL of phosphate bufferpH 6.8 at a temperature of 37±0.5ºC and 50rpm. The formulations were placed in the baskets containing the dissolution medium.

At predetermined time intervals of 10, 20, 30, 40, 50 and 60min, 10mL of samples were withdrawn and replaced with an equal quantity of fresh buffer. The obtained samples were filtered and analyzed by UV-visiblespectrophotometer at 276nm and 244nm for salbutamol sulfate and ambroxol hydrochloride respectively. The cumulative amount of drug release was plotted as a function of time [15].

Kinetic Analysis of Release Data

The *in-vitro* drug release data obtained were treated according to zero-order [R= k/t], first-order [R= k/t], Higuchi [R=K3√t] and Korsmeyers - Peppas [Log=log k4+nlog t] equations, to find the best fit to determine the drug release mechanism [17].

Stability Studies

The product stability can be predicted by subjecting the product under the situation that accelerates the change in a defined and predetermined manner. The stability testing of the formulations wascarried out at 25ºC/75% RH and storage temperature of 2-8ºC for one month. The effects of temperature, humidity and time on the appearance of chocolate and drug content were calculated for assessing the stability of the prepared formulations [18, 19].

Results and Discussion

Drug Excipient Compatibility

FTIR spectra of the drug(s)-excipient mixture illustrated in Figures 1, 2 and 3, retained the characteristic functional peaks of the drugs (salbutamol sulfate and ambroxol hydrochloride) and the excipientsrespectively, which ensured that there was no interaction between the drugs and excipients and there was no significant change in the chemical integrity of the drug.

DSC spectra of salbutamol sulfate, ambroxol hydrochloride, chocolate base and chocolate basewith drug mixture wereshown in Figures 4, 5 and 6 respectively. DSC thermograms of chocolate base displayed a peak at 36.97ºC, salbutamol sulfate indicated a sharp peak with a melting temperature of [T onset= 205.36ºC] and ambroxol hydrochloride showed an endothermic peak at 245.97ºC. These endothermic peaks were also retained in all the mixture of drug-excipients with a little shifting of the peaks, which may be due to the presence of moisture or impurity of the excipients.

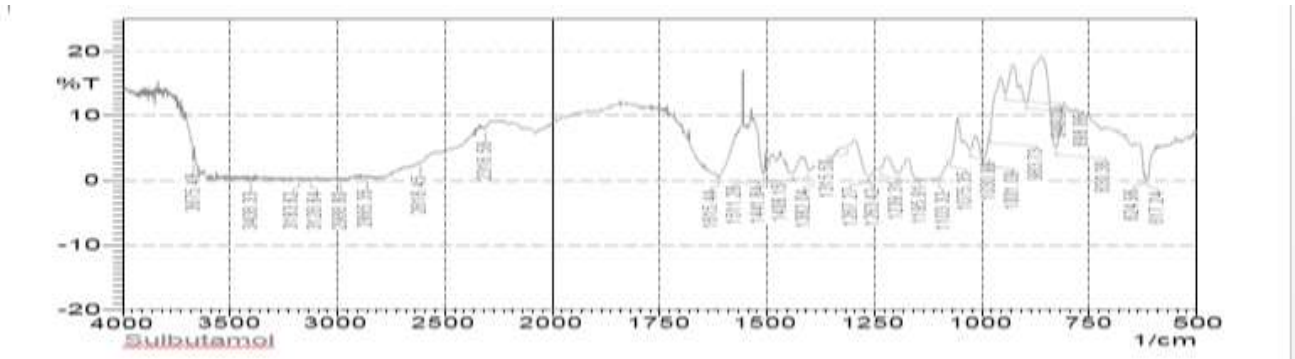

Fig. 1: FTIR spectrum of salbutamol sulfate

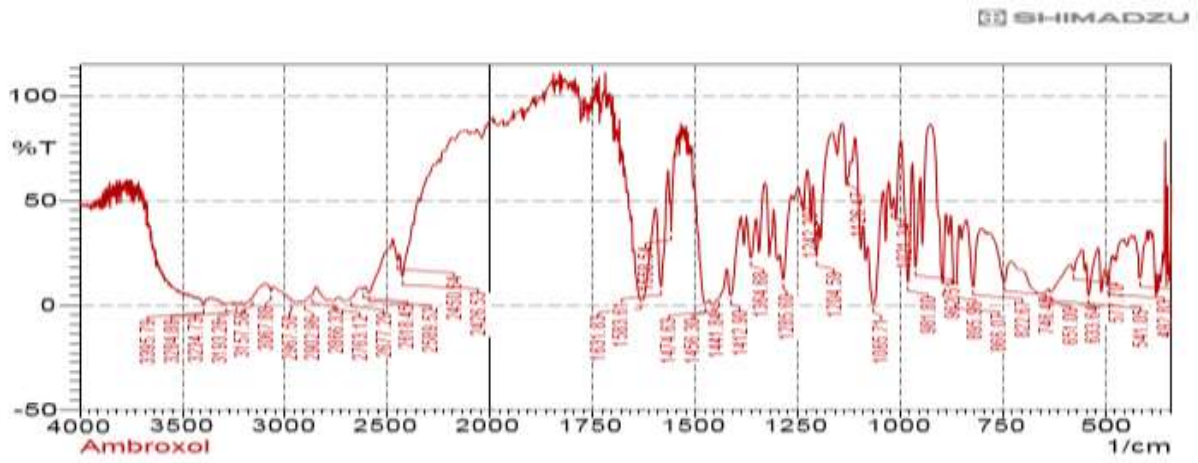

Fig.2: FTIR spectrum of ambroxol hydrochloride

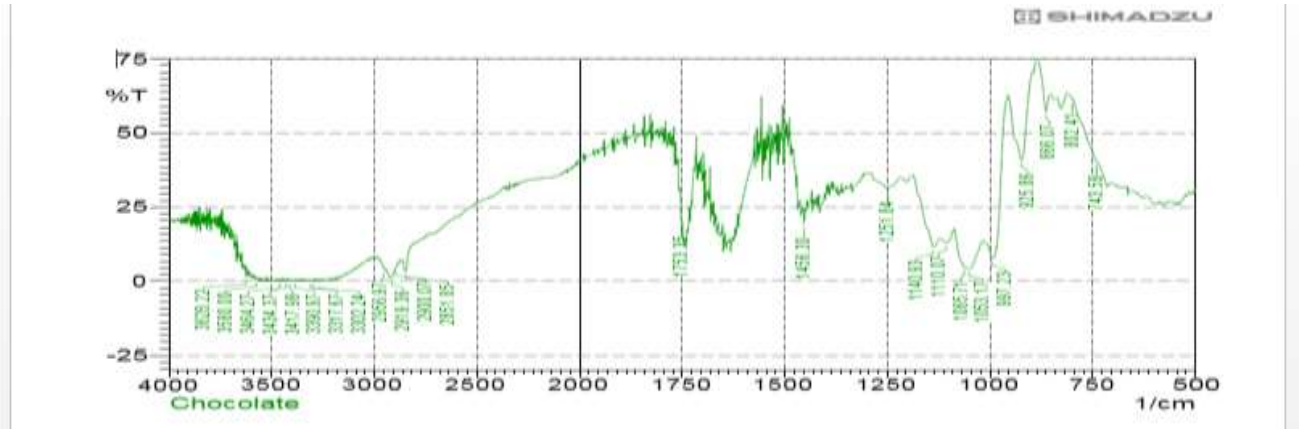

Fig. 3: FTIR spectrum of a physical mixture of drug and excipients used in the chocolate formulation F3

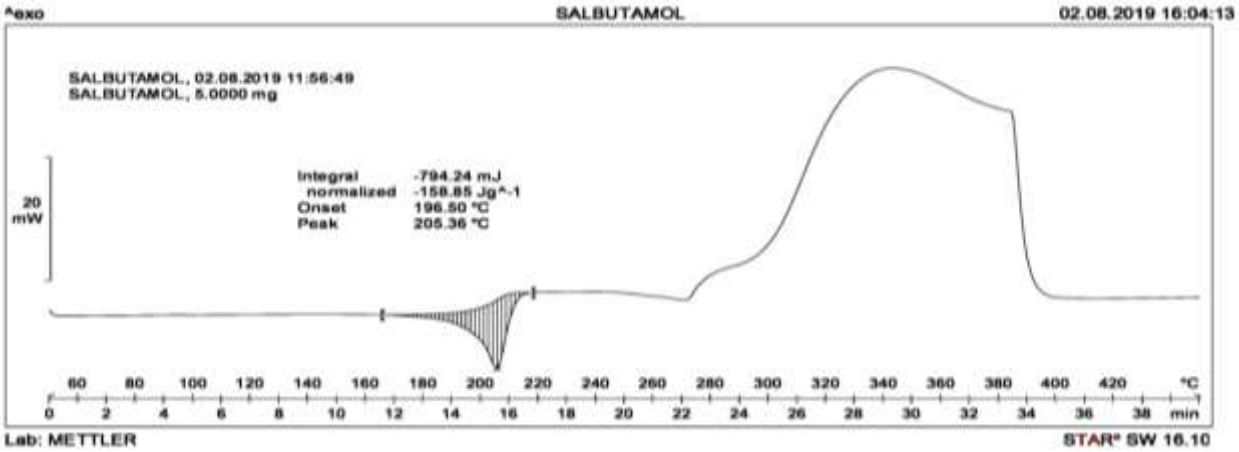

Fig. 4: DSC thermo gram of salbutamol sulfate

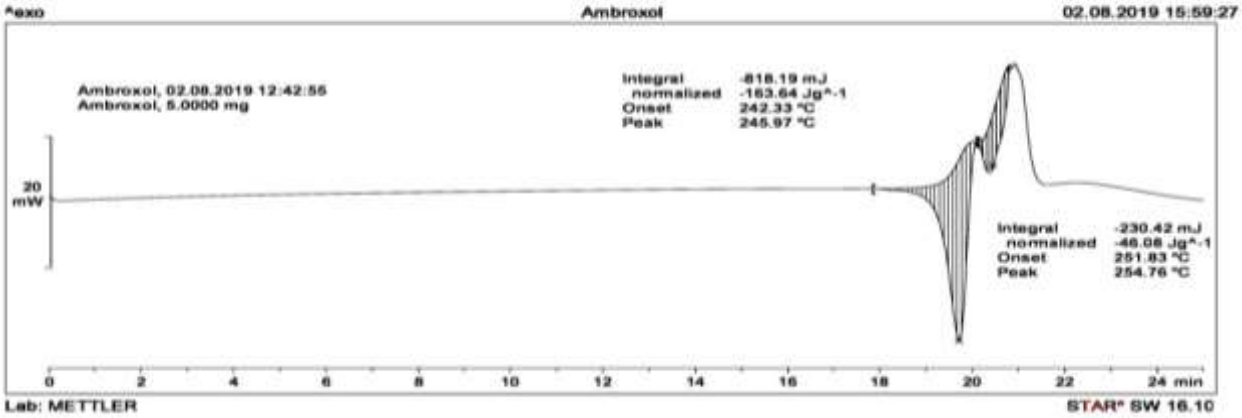

Fig. 5: DSC thermo gram of ambroxol hydrochloride

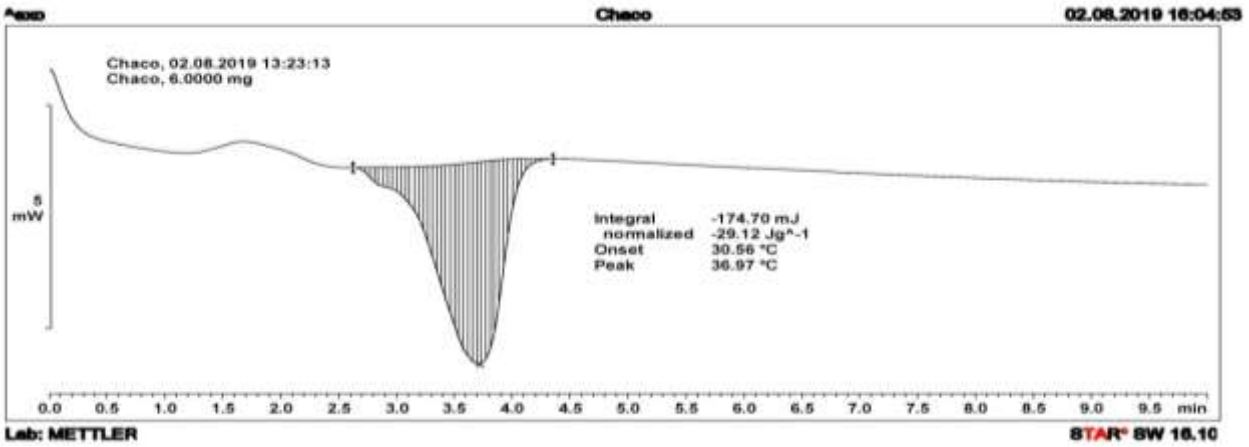

Fig. 6: DSC thermogram of chocolate formulation F3 containing salbutamol sulfate and ambroxol hydrochloride

Calibration Curves of Salbutamol Sulfate and Ambroxol Hydrochloride

A standard curve was constructed using a series of concentrations of drug solutions in phosphate buffer pH 6.8. The absorbance values corresponding to the concentrations were shown in Figure 7 and Figure 8 and the regression values[R^2] were found to be 0.9981and 0.9910 at 276 nm and 244 nm respectively.

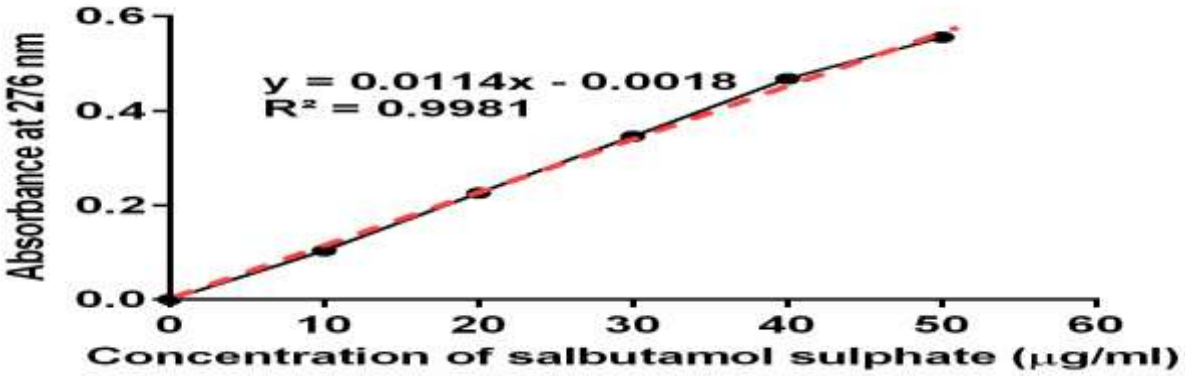

Fig. 7: Calibration curve of salbutamol sulfate at 276nm

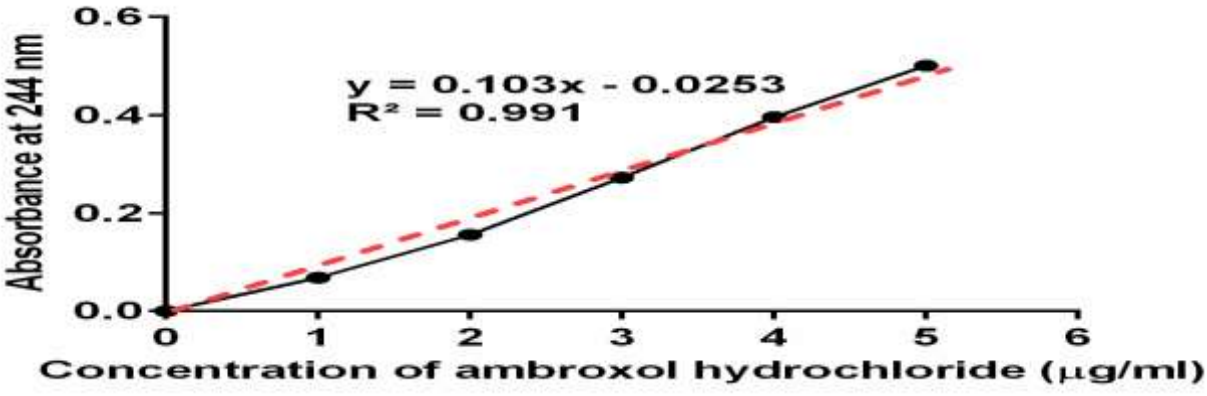

Fig. 8: Calibration curve of ambroxol hydrochloride at 244nm

Solubility Studies

The data for the saturated solubility study in distilled water, phosphate buffer pH 6.8 and pH 7.4 were shown in Table 3. The results of solubility studies indicate that the drug solubility was dependent on pH. The drugs were found to be least soluble in distilled water, which might be due to the unionization of the drugs. The unionized form of the drug enables the permeability of the drug through the membrane but limits the drug solubility. The results indicate that salbutamol sulphate exhibited good solubility in water and ambroxol hydrochloride was sparingly soluble in water.

Melting Point

The melting point was obtained by the capillary method and the results were listed in Table 4. The obtained results match standard values indicating the purity of the drug substances.

Partition Coefficient

Lipophilic and hydrophilic balance is the contributing factor for the rate and extent of drug absorption from a drug delivery system. Partition coefficients of salbutamol sulphate and ambroxol hydrochloride were determined in phosphate buffer pH 6.8 and n-octanol and the results were shown in Table 4. The results indicate that salbutamol sulphate is hydrophilic and ambroxol hydrochloride is lipophilic in nature.

Table 4: Melting point and partition coefficient of the test drugs

Drug	Melting Point [ºC]		Partition Coefficient[log P]
	Experimental values	Standard values	
Salbutamol sulphate	158ºC	157-158ºC	1.40
Ambroxol hydrochloride	234ºC	233.0-234.5ºC	2.65

Characterization of the Chocolate Base

Determination of Viscosity

The viscosity of the chocolate base was found to be 58,200.6 cps±0.62. Viscosity above 5000cps indicated high chocolate viscosity ideal for moulding the chocolate into a specific shape.

Characterization of medicated chocolate

Physical Observation

The control of the overall appearance of chocolate involves the determination of a number of attributes such as chocolate's color, presence or absence of an odor, taste, surface texture and physical flaws. Randomly selected 10 medicated formulations were inspected visually and the results were listed in Table 5. The visual identity and overall elegance of the chocolate play an essential role in consumer acceptance and to control lot to lot uniformity.

Table 5: Physical observation of medicated chocolate

S. No	Characteristics	Result
1	Color	Dark brown
2	Odor	Pleasant
3	Taste	Sweet
4	Texture	Smooth
5	Appearance	Glossy
6	Shape	Heart

Weight Uniformity

Uniformity of weight is an in-process test which ensures the consistency of the dosage unit during moulding process. The variation between medicated chocolate with respect to dose and weight must be reduced to a minimum. The weight of chocolates was found to be 2.06 g for F1, 3.09 g for F2 and 3.09 g for F3, as listed in Table 6. The results indicate that none of the individual chocolate weight deviates from the average weight by more than 5% and it complies with IP standards for tablets.

Thickness

The thickness of the medicated chocolate is influenced by the diameter and the amount of fill in the mold. Six medicated units of chocolates were used to evaluate the average thickness using Vernier caliper. The results show that the thickness of the medicated chocolates was controlled within ±5% variation.

Drug Content

All the prepared medicated chocolate formulations showed uniformity in drug content and were within the acceptable range [97% to 105%], indicating uniformity of drug dispersion in medicated chocolates.

Moisture Content

Moisture content affects the physicochemical and microbiological properties of pharmaceutical finished dosage form.

The results were listed in Table 6 and the

values were found to be ideal for medicated chocolate.

Table 6: Evaluation of formulated medicated chocolates containing salbutamol sulphate and ambroxol hydrochloride

Formulation code	Weight variation in %	Thickness in mm	Moisture content in %	Drug content in %		Bloom test
				Salbutamol Sulphate	Ambroxol Hydrochloride	
F1	5±0.2	8.97±0.02	1.32±0.03	94.7±1.2	95.3±1.8	No blooming was observed
F2	4±0.5	8.36±0.02	1.66±0.02	95.4±1.9	96.2±1.3	
F3	2±0.1	9.16±0.01	1.99±0.02	96.8±2.1	97±1.6	

Bloom Test

The results of fat bloom and sugar bloom were observed in Figure 9. The absence of light color spots or dusty appearance on the medicated chocolates indicates the absence of fat bloom and sugar bloom.

Fig. 9: Images of fat bloom and sugar bloom tests

Selection of Optimized Formulation

Medicated chocolates should possess suitable physicochemical properties to mask the bitter taste. Based on the results obtained from the above studies so far, the formulation F3 was found to be ideal in all characteristics and selected for *in-vitro* release and stability studies.

In-Vitro Drug Release Studies

The *in-vitro* release behavior of salbutamol sulphate and ambroxol hydrochloride was summarized and the cumulative percentage release was shown in Figure 10. The regression values from various kinetic equations were represented in Table 7. The R^2value for the zero-order kinetics was found to be 0.99, which confirmed that the drug release from the dosage form follows zero-order kinetics. Based on the n value and R^2 value, the drug release mechanism from the medicated chocolate was found to be following Fickian transport.

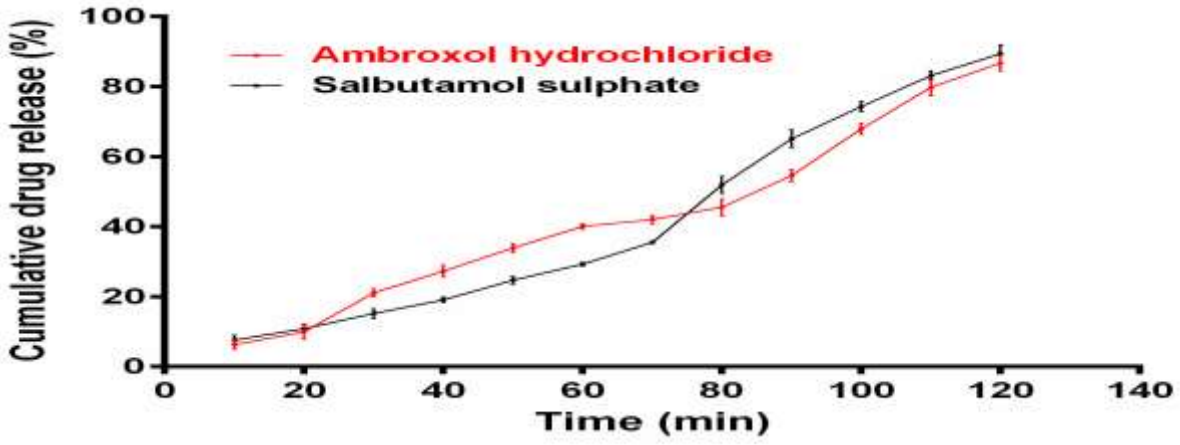

Fig. 10: *In-Vitro* drug release profile of the medicated chocolate formulation F3

Table 7: Release kinetics data of the formulation F3 for salbutamol sulphate and ambroxol hydrochloride

Formulation	Drug	Zero-order	First-order	Higuchi	Korsmeyer-

Code		[r^2 value]	[r^2 value]	[r^2 value]	Peppas[n value]
F3	**Salbutamol sulphate**	0.989	0.838	0.882	1.06
	Ambroxol hydrochloride	0.991	0.851	0.931	1.05

Stability Studies

The medicated chocolates were evaluated for physical and chemical stability over a period of a month at room temperature. No significant changes in the physical and chemical properties were observed, which indicates that the formulated medicated chocolates were stable, the physical evaluations were reported in Table 8

Table 8: Evaluation of physical characteristics of the medicated chocolate formulation after accelerated stability studies

Days &Temperature		Color	Odor	Appearance	Bloom
07 days	25℃/75RH	Dark brown	Pleasant	Glossy	Absent
	2℃ to 8℃	Dark brown	Pleasant	Glossy	Absent
15 days	25℃/75RH	Dark brown	Pleasant	Glossy	Absent
	2℃ to 8℃	Dark brown	Pleasant	Glossy	Absent
30 days	25℃/75RH	Dark brown	Pleasant	Glossy	Absent
	2℃ to 8℃	Dark brown	Pleasant	Glossy	Absent

Conclusion

The fabricated chocolate was elegant, smooth and creamy in texture and was excellent for masking unpleasanttaste and feels associated with the drugs and excipients. It can deliver the medicament through oral drug delivery in a palatable manner. Thus, delivering the drug[s] in chocolate form may improve patient compliance as it can be used easily by pediatric patients with high preference.

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