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Open Access Research Article

DEVELOPMENT AND *IN-VITRO* EVALUATION OF CANDY BASED MEDICATED LOLLIPOPS: A NOVEL SYSTEM OF DRUG DELIVERY

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ABSTRACT

Lollipops or lozenges are defined as the flavored medicated dosage forms intended to be sucked and held in the mouth or pharynx containing one or more medicaments usually in the sweetened base. Lollipops are commonly used for the purpose of local or systemic effects through the buccal mucosa. Advantages of the lollipop as dosage forms include increase in bioavailability, reduction in dose size, gastric irritation and bypass first metabolism[1]. Lollipop is designed to improve patient compliance, acceptability, transportation etc[2]The lollipops were prepared by heating and congealing method in a candy based industry with sucrose base. All the formulations prepared were subjected to various physicochemical parameters like hardness, content uniformity, friability, weight variation etc. Thickness of lollipop ranges from 12-13.2 mm. The hardness of these lollipops ranges between 10-11.5 kg/cm... Results of in-vitro release profile indicated that formulation L3, L6, and L10 were the most promising formulations as the extent of drug release from this formulation was high as compare to other formulations up to 30 mins. The *in vitro* release of medicated lollipop of ambroxol HCl was found in the release of drug from the lollipop depends on the type and concentration of polymer used. As per all satisfactory evaluation parameters, the batch L3 is found to be optimized batch. The stability studies showed that there was no change in the formulation after 90 days. The medicated lollipops can provide an attractive alternative formulation in the treatment of mucolytics in pediatric patients.

Keywords: Amboxol HCl, Lollipops, mucolytic and mucokinetics.

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INTRODUCTION

Lollipops or lozenges are defined as 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. Lollipops are commonly used for the purpose of local or systemic effects through the buccal mucosa. Advantages of the lollipop as dosage forms include increase in bioavailability, reduction in dose size, gastric irritation and bypass first metabolism[1]. Lollipop is designed to improve patient compliance, acceptability, transportation etc [2,3]. For the past two decades, there has been an enhanced demand for more patient compliance dosage forms. As a result, the demand for their technologies has been increasing three-fold annually. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are now focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects[4]. The advantages of this formulation are easy to administer to both paediatric as well as geriatric patients and Systemic absorption of drugs can be possible through buccal cavity. Drug candidates which can be incorporated in lollipop, belong to one of the following categories: Antiseptics, Local anaesthetics, Antibiotics, Antihistaminics, Antitusives, Analgesics, Decongestant, Antifungal.

Classification of lozenges

Lozenges can be classified into various classes based on various methods like

(A) According to the site of action

(a) Local effect

Ex. Antiseptics, Decongestants.

(b) Systemic effect

Ex. Vitamins, Nicotine.

(B) According to texture and composition

(a) Chewy or caramel based medicated Lozenges
(b) Compressed tablet lozenges
(c) Soft lozenges
(d) Hard lozenges

Hard Candy Lozenges or lollipop:

Hard candy lozenges are mixtures of sugar and other carbohydrates in an amorphous (noncrystalline) or glassy state. They can also be regarded as solid syrups of sugars. The moisture content and weight of hard candy lozenge should be between, 0.5 to 1.5% and 1.5-4.5g respectively. These should undergo a slow and uniform dissolution or erosion over 5-10min., and should not disintegrate. The temperature requirements for their preparation is usually high hence heat labile materials cannot be incorporated in them[5,6]. The ingredients for hard candy lozenges include body agent or base which is corn syrup that is available on Baume basis. A 43° Baume corn syrup is preferred in hard candy lozenges. Sweetening agents such as sucrose, dextrose, maltose and lactose are added. Acidulents are added to candy base to strengthening the flavor characteristics of the finished product. Commonly used acids are citric, tartaric, fumaric and malic acid. Colours include FD & C colours, orange colour paste, red colour cubes etc while flavours used include menthol, eucalyptus oil, spearmint, cherry flavor etc. Medicaments up to 2-4% can be incorporated in the hard candy lozenges. Salvage solution can be liquid or solid5.

METHODS

Preformulation Studies of Drug [7]

Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation studies are the first step in the rational development of dosage form of a drug substance. The goals of the program therefore are To establish the necessary physicochemical characteristics of a new drug substance. To establish its compatibility with different excipients.

Characterization of Ambroxol HCL:

Organoleptic properties [8]

The drug powder was analyzed for color, odor and taste.

Description [8]

The drug sample (Ambroxol HCl) was analyzed for physical appearance and powder nature.

Melting point [8]

Melting point determination of Ambroxol HCl was done by open capillary method. It is a good first indication of purity of sample since the presence of relatively small amount of impurity can be detected by a lowering as well as widening of melting point range.

Solubility Characteristics

A semi quantitative determination of solubility can be made by adding a solute in small incremental amount to fixed volume of solvents, phosphate buffer pH 6.8, sparingly soluble in water, soluble in methanol, practically insoluble in methylene chloride. After each addition, the system is vigorously shaken and examined usually for any undissolve particles

Spectroscopy

UV-visible Spectroscopy[9]

Determination of λ max

The UV absorption spectrum of Ambroxol HCL was obtained using a UV-visible Spectrophotometer. The spectrum was scanned from 200 nm to 400 nm. A typical spectrum of Ambroxol HCl dissolved in phosphate buffer 6.8 (Conc. 100µg/ml) is shown in fig 2.

Preparation of Standard Stock Solution

Standard stock solution of Ambroxol Hydrochloride were prepared by dissolving 10 mg of AMB separately in 10 ml of 6.8 pH Phosphate buffer solution and sonicated for 15 minutes and filtered through whatman filter paper in order to get dilution of 1 mg/1 ml i.e.1000 µg/ml.

Determination of Absorption Maximas

By appropriate dilution of standard stock solutions of Ambroxol Hydrochloride with 6.8 pH phosphate buffer solution containing and 10 µg/ml of Ambroxol Hydrochloride was scanned separately in the range of 200-400nm. Wavelength of absorption maxima was determined for drugs. Ambroxol HCL showed absorption maxima one at 245 nm.

Preparation of calibration curve for Ambroxol HCL

Concentration was made using the phosphate buffer pH 6.8 media. It was analyzed spectrophotometrically by measuring the absorbance at 245 nm wavelength. The fig 1 shows standard calibration curves with slope 0.026 and regression value 0.9999. The curve was found to be linear in the range 2-18 µg/ml at .the drug solution of with concentration of 100µg/ml was prepared. Serial dilution 2, 4....18µg/ml

IR Spectroscopy

The IR spectrum of drug & excipients was obtained in a KBR pellet using Shimadzue 206-7350038 FT-IR spectrophotometer. FT-IR spectra were recorded in the region of 400–4,000 cm^{-1}. Assign the major absorption bands change in absorption bands indicates incompatibility between drug & excipients.

Formulation of medicated lollipop:

Table 1: Formulation table for medicated lollipop

Ingredients In mg	L0	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10
Ambroxol HCl	*15*	*15*	*15*	*15*	*15*	*15*	*15*	*15*	*15*	*15*	*15*
Sucrose	*3523*	*3490*	*3465*	*3440*	*3490*	*3465*	*3440*	*3465*	*3440*	*3465*	*3440*
Dextrose	*1420*	*1420*	*1420*	*1420*	*1420*	*1420*	*1420*	*1420*	*1420*	*1420*	*1420*
Citric acid	*50*	*50*	*50*	*50*	*50*	*50*	*50*	*50*	*50*	*50*	*50*
Methyl cellulose	-	*25*	*50*	*75*	-	-	-	-	-	-	-
Scmc	-	-	-	-	*25*	*50*	*75*	-	-	-	-
Hpmc k100m	-	-	-	-	-	-	-	*50*	*75*	-	-
Hpmc k4 m	-	-	-	-	-	-	-	-	-	*50*	*75*
Colouring agent	*Quantity sufficient*										
Flavouring agent	*Quantity sufficient*										
PurifiedH_2O	*Quantity sufficient*										

Preparation of syrup base:

Syrup base was prepared by dissolving 66.66%w/v sucrose in purified water at 110°c and continuously stirring for about 90 min.

Preparation of medicated Lollipops[10]:

Medicated lollipops of 5 gms were prepared. The Method followed for the preparation was heating and congealing technique. Syrupy base was prepared in a beaker dissolving the required amounts of sucrose in water on heating and stirring at 110°C for about 90 min. Dextrose was added and stirring continued for 2 hrs by raising the temperature to 160°C. The material was transferred to a cooling slab and temperature was brought down 90°C till a plastic mass was obtained. Drug, polymer, colour, flavour were added and mixed the material for 30 min. The material was size roped on moving rollers which were then sized into 5gms. Lollipops and air dried for about 2 hrs. in drying chamber. The prepared lollipops were seal wrapped in polythene wrappings. An altogether three batches of formulations were prepared i.e., without added hydrocolloid, hydroxy propyl methyl cellulose (HPMC) K4M and K100M, methyl cellulose, carboxy methyl cellulose sodium salt added medicated lollipops.

RESULTS AND DISCUSSION

Characterization of Ambroxol HCl

Organoleptic characterization and Melting point determination

The physicochemical characteristics of Ambroxol HCL are described in Table 2.

Table 2: Physicochemical Characteristics of Ambroxol HCL.

Sr. no.	Test	Observation
1.	Colour	White to yellowish crystalline powder
2.	Odour	Odourless
3.	Taste	Bitter
5.	Melting point	233-234.5
6.	pH	4.5-6.0

The organoleptic character and melting point was found to be as per standard drug so drug used in the formulation was found to be pure according to I.P. specification.

Solubility analysis:

Table 3: Solubility profile of Ambroxol HCl

Sr. No.	Solvent	Solubility
1.	Water	Sparingly soluble
2.	Buffer solution 6.8	Soluble
3.	Methanol	Soluble

The solubility of pure drug in 10mg/10ml of solvent was carried out and it reveals that it is soluble in methanol, sparingly soluble in water, soluble in phosphate buffer ph 6.8.

Standard calibration curve of ambroxol HCL in phosphate buffer 6.8:

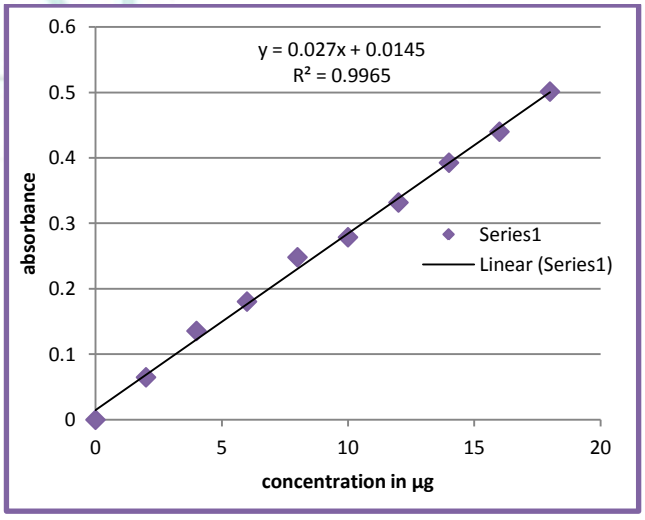

Figure 1: Calibration curve of ambroxol HCl in pH 6.8

Determination of λmax:

The UV spectrum of ambroxol HCL in phosphate buffer 6.8 showed maximum absorption at 245 nm. Hence drug used in the formulation was found to be pure. The UV

spectrum of the ambroxol HCL in phosphate buffer 6.8 is given in Figure: 2.

IR ANALYSIS:

In the spectral analysis of pure ambroxol hcl , N-H streching of primary amine, C-H streching , C-5 Streching , C-H deformation , N-H out of plain bending of pure ambroxol HCl. The ambroxol hcl with polymer was almost in the same region of the wave number ranging from 608 cm^{-1}- 3402 cm^{-1}. It showed that there was no significant interaction between the drug and polymer compatible with each other.

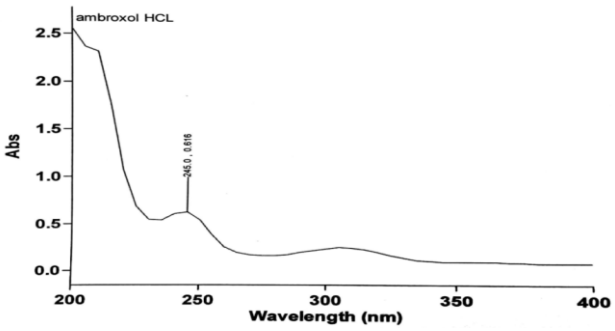

Figure 2: λ_{Max} of ambroxol hydrochloride

IR spectra of ambroxol HCl:

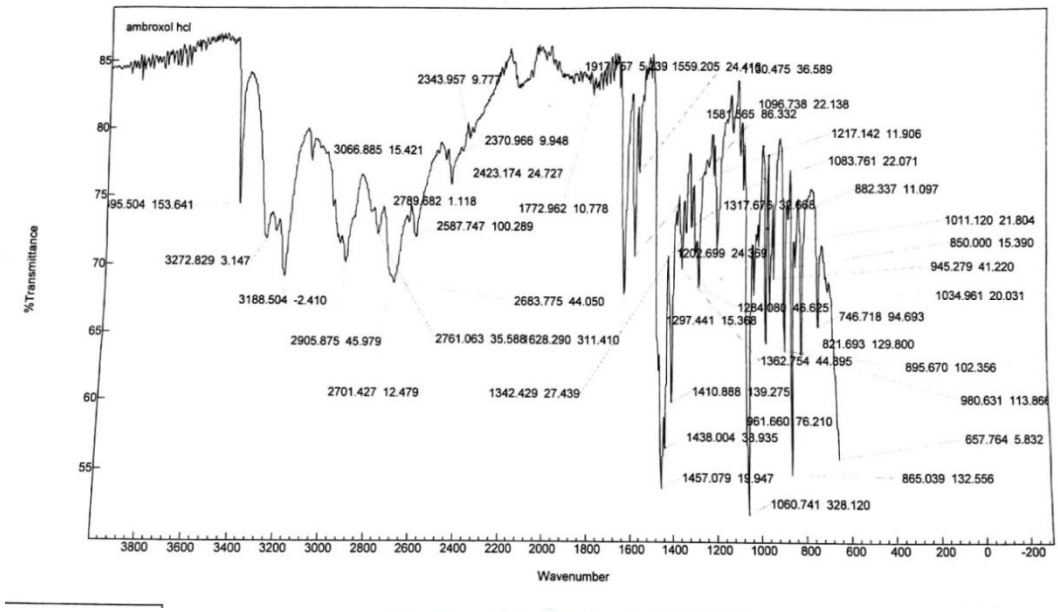

Figure 3: IR Spectra of ambroxol hydrochloride

Compatibility study of Ambroxol HCl and SCMC:

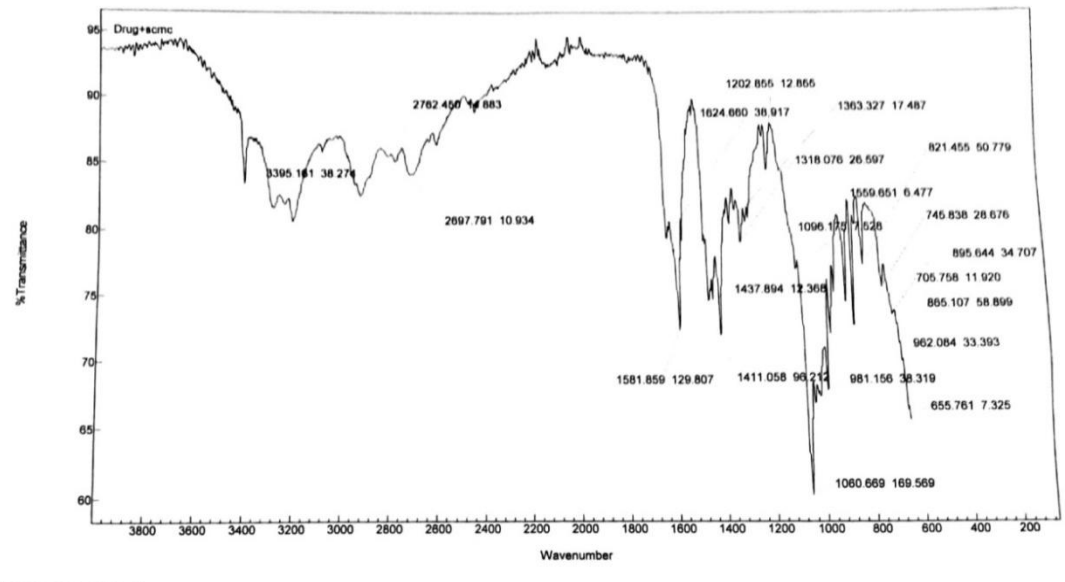

Figure 4: IR Spectra of ambroxol hydrochloride and SCMC

Compatibility study of Ambroxol HCl and HPMC K100M

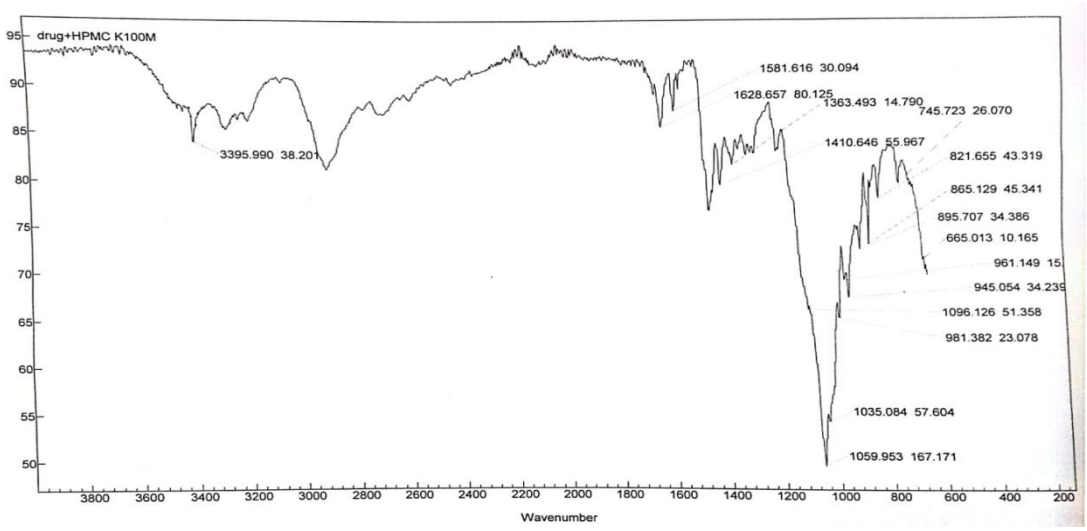

Figure 5: IR Spectra of ambroxol hydrochloride and HPMC K100M

Compatibility study of ambroxol HCl and HPMC K4M

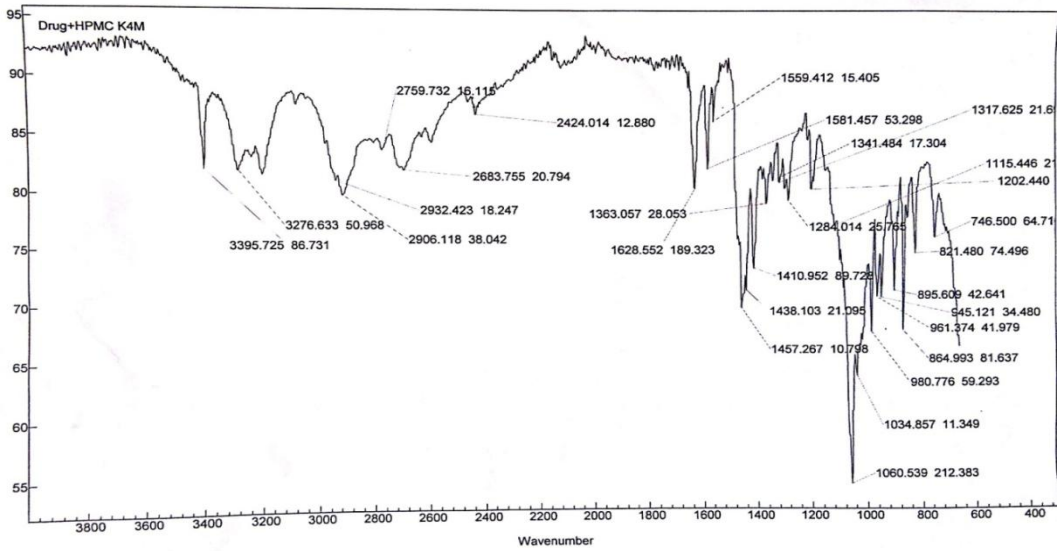

Figure 6: IR Spectra of ambroxol hydrochloride and HPMCK4M

Compatibility study of ambroxol HCl and methyl cellulose:

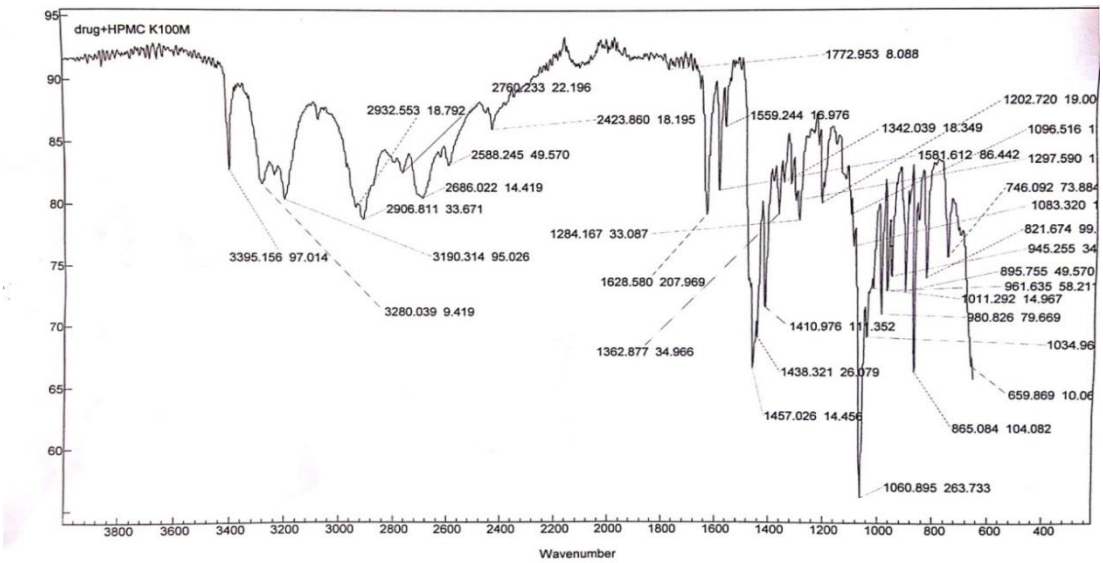

Figure 7: IR Spectra of ambroxol hydrochloride and methyl cellulose

Characterization of prepared medicated lollipops:

Table 4: Appearance of medicated lollipops

Formulation	Appearance
L0-L10	Orange, hard, little sticky, easily removed by mold

Evaluation of Ambroxol HCL medicated lollipops:

Table 5: Standard physical tests for medicated lollipops (L0-L5)

Formulation	Thickness (mm)±S.D	Hardness (kg/cm2)±S.D	Friability (%)±S.D	Weight Variation (gm)±S.D	Moisture content ± S.D
L0	12.6±0.33	11±0.23	0.6±0.033	5±0.41	0.5±0.02
L1	13.2±0.32	11±0.40	0.5±0.041	4.33±0.05	0.6±0.06
L2	12.7±0.38	10±0.40	0.7±0.012	5.09±0.06	0.8±0.023
L3	12.9±0.14	10.5±0.23	0.56±0.044	4.99±0.04	0.4±0.012
L4	12.1±0.31	10.7±0.12	0.74±0.061	5±0.11	0.6±0.052
L5`	12.6±0.12	10.5±0.23	0.56±0.044	4.98±0.15	0.42±00.11

Table 6: Standard physical tests for medicated lollipops (L6-L10)

Formul^{n}	Thickness(mm)±S.D	Hardness (kg/cm2)±S.D	Friability (%)±S.D	Weight Variation (gm)±S.D	Moisture content ± S.D
L6	12.8±0.40	11±0.23	0.67±0.057	4.88±0.05	0.5±0.02
L7	12.5±0.12	11±0.23	0.69±0.021	4.9±0.12	0.3±0.32
L8	12.4±0.09	10±0.23	0.78±0.057	5.05±0.44	0.4±0.0.23
L9	12.0±0.37	11.5±0.62	0.98±0.043	5±0.1	0.5±0.025
L10	12.6±0.33	10±0.40	0.56±0.109	4.67±1.77	0.6±0.11

Lollipops of all formulations (F0 to F10) were evaluated for different parameters such as thickness, hardness, weight variation, drug content and friability and results are shown in 5 and 6.

Hardness: Hardness values of the formulation ranged from 10-11.5 kg/cm2, which indicate good strength of lollipop.

Friability: Friability values of all the formulation were less than 1%, indicating good strength of lollipops. .

Weight variation: In weight variation test, the Pharmacopoeial limit for percent of deviation for tablets weighing between 5.25-4.75 is not more than 5%. The average percent deviation of all tablets was found to be within the limit and hence all formulation passes the weight variation test.

Thickness: Examination of lollipops from each batch showed flat circular shape with no cracks having orange colour. The thickness of lollipops was determined using Vernier caliper. The thickness of lollipops ranged from 12-13.2 mm. All formulations showed uniform thickness.

Moisture analysis: Moisture content in the given lollipops ranged from 0.3±0.32-0.6±0.11.

Content uniformity: The drug content was found to be uniform among all formulation and ranged from 90.22 - 99.44.

Table 7: Content uniformity of medicated lollipops (L0-L4)

Batch no.	L0	L1	L2	L3	L4	L5	L6	L7	L8	L9
Drug content (%)±S.D	96.99	96.52	95.65	99.44	98.23	93.22	97.66	95.45	96.74	93.34

8.6 *In-vitro* drug release studies:

The dissolution rate was studied using 100ml for followed by phosphate buffer (pH 6.8) for the remaining hours under sink condition using USP dissolution apparatus type II. The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in predetermine manner.

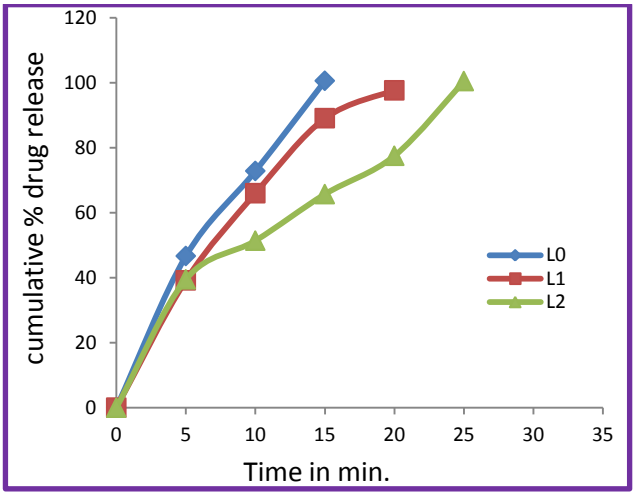

Figure 8: *In-vitro* dissolution profile of L0, L1 and L2 formulation

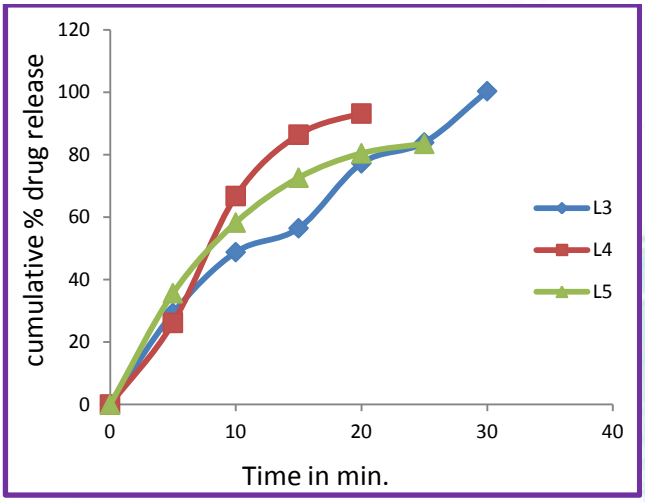

Figure 9: *In-vitro* dissolution profile of L3, L4 and L5formulation

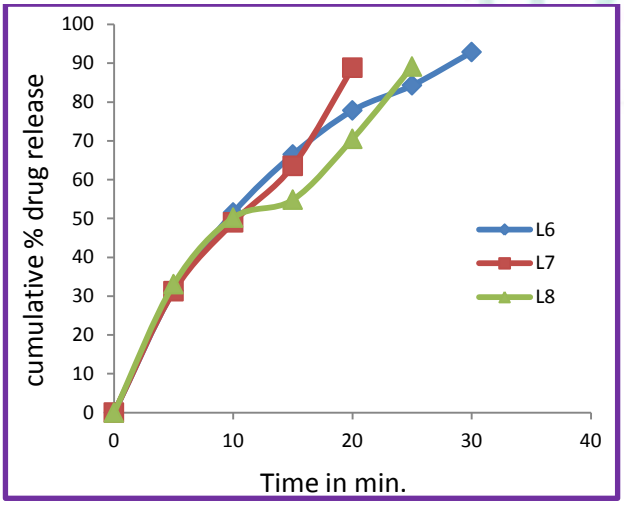

Figure 10: *In-vitro* dissolution profile of L6, L7 and L8formulation

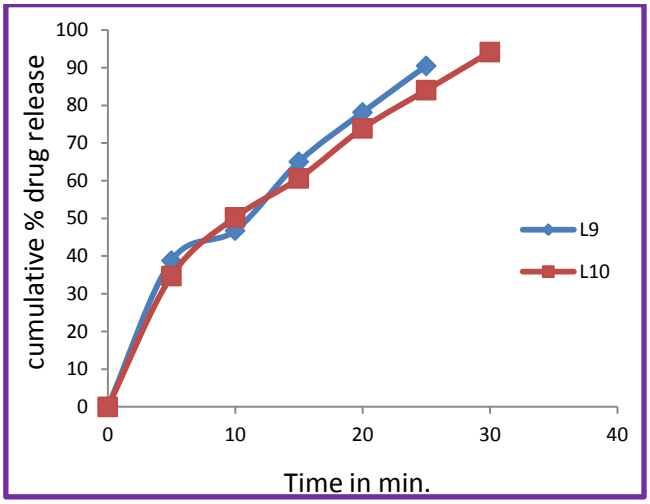

Figure 11: *In-vitro* dissolution profile of L9and L10 formulation

All the 11 formulation prepared were subjected to *in-vitro* release study. The *in-vitro* method for studying the release rate should be so that it must simulate the mouth condition. In the present work *in-vitro* release study was carried out using dissolution apparatus. For different time interval, sample was withdrawn and cumulative drug release was calculated. The dissolution apparatus USP II paddle type was used. The temperature was maintained at 37± 0.5 0C and stirred at 100rpm. The dissolution medium being phosphate buffer of pH 6.8. The samples were withdrawn at 5mins interval for 30mins. Since the drug release in the formulations F0 were faster because this batch are without polymer. Cumulative percentage drug release is calculated. The results are given in Table 8 and Figure 8 to 12. The cumulative percentage drug release of L0 at the end of 15 minutes was found to be 100.59±0.50% at the end of 20 minutes. The release was faster in L0 than L1. L1, L2, L3 containing the methyl cellulose polymer with different conc. (25mg, 50mg, 75 mg). The cumulative percentage drug release of L1 97.65±1.00 at the end of 20 minutes, L2 was 100.05±0.16% by the end of 25mins and in L3 was 100.36±0.22 at 30mins.L4, L5, L6 containing SCMC polymer with different conc. (25, 50,75 mg) .L4 was93.19±0.64 in 20 min. L5 was 83.49±0.21 and L6 was 92.86 ±0.40. L7 and L8 contains HPMC K100polymer with two conc. (50mg,75mg) L7 was 88.83±0.67,L8 was 89.13±0.18. L9 and L10 containing HPMC K4M with two conc. (50mg, 75mg). L9 was 90.47±1.09 and L10 was 94.14±0.38.

Hence by the determination of the in-vitro release data, it can be concluded that the drug release was faster in case of L0 without polymer. The formulations containing Sodium carboxy methyl cellulose and Hydroxy propyl methyl cellulose K4 M & K100M showed slower release rates when compared to M.C. The use of polymers showed extended release of the drug. Methyl cellulose (75 mg) containing lollipop gives the extended release up to 30 min and gives the 100.36±0.22 cumulative% drug release

Table 8: Parameters studied on L3, L6, L10 formulations before and after stability study

Parameters	Before stability study			After stability study		
	L3	L6	L10	L3	L6	L10
Thickness	12.9±0.14	12.8±0.40	12.6±0.33	12.9±0.14	12.8±0.40	12.6±0.33
Hardness	10.5±0.23	11±0.23	10±0.40	10.5±0.23	11±0.23	10±0.40
Drug content	99.44%	97.66%	98.63%	99.44%	97.66%	98.63%
Moisture analysis	0.4±0.012	0.6±0.052	0.5±0.02	0.4±0.024	0.6±0.045	0.5±0.32

*All the values are represents as Mean ± S. D. (n=3)

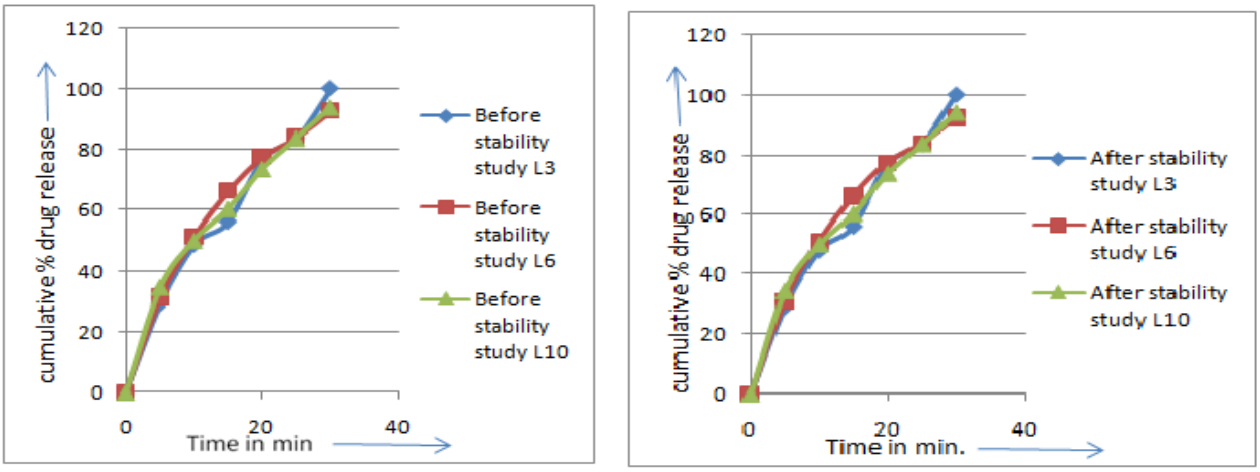

Figure 12: Dissolution profile of formulations L3, L6 and L10 before and after stability study

SUMMARY

In this present study attempt was made to prepare the medicated lollipop for peadiatrics containing mucolytic and mucokinetic ambroxol HCl to enhance the release rate were prepared using methyl Cellulose, HPMC K4M, HPMC K 100M & SCMC by heating and congealing method using various ratios. The obtained Lollipops were flat spherical and uniform in shape and size.The lollipops were evaluated for various parameters. Thickness of lollipop ranges from 12-13.2 mm. The hardness of these lollipops ranges between 10-11.5 kg/cm. Percentage buoyancy was in the range of 83.59-100.56% Results of the *in vitro* drug release indicated that the ambroxol HCl released in 30 mins. Results of in-vitro release profile indicated that formulation L3, L6, and L10 were the most promising formulations as the extent of drug release from this formulation was high as compare to other formulations up to 30 mins. The *in vitro* release of medicated lollipop of ambroxol HCl was found in the release of drug from the lollipop depends on the type and concentration of polymer used. As per all satisfactory evaluation parameters, the batch L3 is found to be optimized batch. The stability studies showed that there was no change in the formulation after 90 days.by adding the various polymers increasing the release rate by using different conc. of polymers

Thus cost effective and slow release medicated lollipop of ambroxol HCl in oral cavity is a safe and effective dosage form for pediatrics and having better bioavailability.

CONCLUSION

It can be concluded that medicated lollipop for pediatrics' are medicated confections designed totally deliver drug to mouth and throat for the treatment of respiratory tract infection. In the study of drug and compatibility is concluded that the drug is compatible with the polymers. The various physicochemical properties like solubility, colour, odor, taste, pH, melting point are evaluated successfully. In in-vitro drug release analysis observed that those formulation containing polymers that gives better effect than without polymers. Formulation showed best drug release extended up to 30 min, compatible nature and good stability, so it can be a better effective formulation in pediatrics. Formulation showed better stability than other formulation. Pediatrics attracts towards this formulation and in dysphagia this formulation are more convenient. So, these novel medicated lollipops can make better reliability for the efficient treatment.

.Most of the ambroxol HCl formulations are available, but by developing formulation we can improve stability of formulation, fixed dosing ,increase patient compliance & also bioavailability of drug.

Future scope

- *In-vivo* study
- *In-vivo in- vitro* correlation
- Formulating various formulation using different polymers those extended the drug release.
- Formulating various formulation containing combination of drugs are used.

Formulating this formulation for the treatment of various problems in paediatrics.

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