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Design and Development of Medicated Lollipop Containing Albendazole

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ABSTRACT

The present work is aimed at Design and development of medicated lollipop containing Albendazole. One of the major health problems faced by hundreds of millions of school-age children is infection by helminths, more commonly known as worms. Albendazole is used as abroad-spectrum anthelmintic. The conventional dosage forms like tablets, capsules, syrups etc are inconvenient for paediatric, geriatric, bedridden patients because of difficult to swallow tablets and capsules or unpleasant taste of drug. As a result, the demand for developing new technologies has been increasing day by day. Lollipops 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. Medicated lollipop is designed to improve patient compliance and increase oral retention time. The lollipops were prepared by heating and congealing method using hydroxypropylmethylcelluloseK4M as polymer. Drug-excipient compatibility study was carried out using FTIR. All the formulations were subjected to various physicochemical evaluations like weight variation, hardness, drug content, friability etc. The *in-vitro* dissolution study of F3 was carried out by two method a) Paddle method b) flow through cell method .The *in-vitro* permeation study of F3 was found to be 72.2% at 30 min. Stability study was carried out as per ICH-Guidelines (Q1A) at 25±2^{o}C/60±5% RH and 40±2^{o}C/75±5% RH . From the present study it can be concluded that addition of hydrophilic polymers yield good result to prolong oral retention time of lollipop.

Keywords: Medicated lollipop, Albendazole, Hydroxypropylmethylcellulose(HPMC K4M)

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INTRODUCTION

One of the major health problems faced by hundreds of millions of school-age children is infection by helminths, more commonly known as worms[1].Secondary disease manifestations dueto the soil-transmitted helminths are varied ranging from malnutrition to respiratory complications. It is probable that protein energy malnutrition and iron-deficiency anemia cause severe morbidity and growth retardation among children[2]. Albendazole is a broad-spectrum anthelmintic. It bind to β-tubulin of the parasite with high affinity and inhibit the synthesis of microtubules. These microtubules are essential for several metabolic processes in the parasite. These decreases glucose uptake in the parasite which leads to parasite death[3].Oral administration is the most popular route due to ease of ingestion, pain avoidance and most importantly patient compliance. Traditional tablets and capsules are inconvenient for pediatric patients because of difficult to swallow it or unpleasant taste of liquid dosage forms. Since from past decade, there has been an increased demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing day by day[4]. Lollipops 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[5].It is found that sucrose based medicated lollipops will be an alternative dosage forms for paediatric patients[6].

MATERIALS AND METHODS

Albendazole, Hydroxypropylmethylcellulose K4M was procured from Yarrow chem. Products Mumbai, Sucrose, dextrose, Citric acid were procured from Himedia Mumbai, Vanilla flavouring agent and Colouring agent were procured from Classics aromatics.

Preparation of medicated lollipop of albendazole:

Heating and congealing method[7,8]: Required quantity of sugar syrup was prepared mixing sugar and water. Dextrose was dissolved in small quantity of water and heated it to 110^0C till dextrose dissolves completely forming as clear viscous syrup. Then the dextrose syrup was poured in to the sugar syrup and heated to 160^0C till the colour changes to golden yellow. Flavour was added between 120^0C to 135^0C then temperature was bought down to 90^0C and drug, polymer and other ingredients were added and mixed it well. The prepared mixture was poured in to the calibrated mould an kept it for air dry for 1-2 hr .The prepared lollipop were stored wrapped in aluminium foil and stored in desiccators to prevent moisture uptake.

Table1:Formulation chart for medicated lollipop

Ingredients	F0	F1	F2	F3	F4
Albendazole(mg)	300	300	300	300	300
Methylcellulose(mg)	-	300	400	-	-
HPMC K4M(mg)	-	-	-	300	400
Sucrose(mg)	3250	2950	2850	2750	2650
Dextrose(mg)	1400	1400	1400	1400	1400
Citric acid(mg)	50	50	50	50	50
Vanilla flavour	qs	qs	qs	qs	qs
Total weight(gm)	5	5	5	5	5

Drug-excipient interaction study[9]:

For studying drug-excipients interaction, prepared lollipops will be subjected for FTIR studies.

Weight variation[9]:

The weight variation conducted by weighing 10 lollipops individually and calculating the average weight and comparing the individual lollipops weight to the average value.

Thickness[9]:

The thickness of 10 lollipops was measured using Venier calipers. lollipops from each batch were selected and evaluated, and the average value with standard deviation was recorded.

Hardness[9]:

Hardness of lollipops was determined by using Monsanto tablet hardness tester .lollipops from each batch were selected and evaluated, and the average value with standard deviation was recorded.

Friability (F) [10]:

Friability of the lollipops was determined using Roche friabilator. The weighed lollipops were placed in the friabilator and operates for 4 min at 25 rpm . The lollipops are then made free from dust and reweighed . The percentage friability is calculated by using formula.

$$F = (W_{initial} - W_{final}/W_{initial}) \times 100$$

Drug content[9]:

10 lollipops were selected randomly and powdered. A quantity of these powder corresponding to 300mg of Albendazole was dissolved in 100ml of PBS pH 6.8 in a 100ml volumetric flask(stock solution "A"). From(stock solution "A") 1ml is diluted with PBS pH 6.8 upto 100ml volumetric flask(stock solution "B"). From(stock solution "B") 1ml is diluted with PBS pH 6.8 upto 10ml volumetric flask(stock solution "C") and absorbance will be recorded at λmax.

***In-vitro* dissolution study for medicated lollipops:**

PADDLE METHOD[9]:

In-vitro release studies were carried using USP-II dissolution apparatus. 900ml of PBS pH 6.8 at 37± 0.5°C is taken as dissolution media. The rpm of the paddle was fixed at 100. Aliquot of 10ml was withdrawn at an interval of 5min up to 30min and absorbance was recorded at λmax.

FLOW THROUGH METHOD[11]:

A Flow through cell dissolution model assembly was designed in our laboratory which maintains perfect sink conditions facilitating better i*n-vitro* evaluation. A intravenous infusion set was attached to a bottle containing PBS pH 6.8. The flow rate was adjusted to 2ml/min using a flow regulator. 10ml of PBS was always maintained in the donor cell containing lollipop throughout the experiment. The lollipop was supported on a small mesh (#40) in the donor cell of the infusion set. The flow of the release medium was the PBS bottle through the lollipop containing cell and to the receiver. The samples 10ml was withdrawn at an interval of 5min up to 30 min and absorbance was recorded at λmax.

***In-vitro* permeation study[12]:**

In-vitro permeation studies were conducted by using Franz diffusion assembly. 100mg equivalent weight of lollipop was placed in dialysis membrane between donor and receptor compartment of diffusion cell assembly. The receptor compartment was filled with PBS pH 6.8, Magnetically stirred at 200 rpm.10ml of samples were withdrawn at suitable time interval from donor compartment. The percentage of Albendazole permeated was determined by measuring the absorbance in UV spectrophotometer at λmax.

Stability study[13]:

Stability study was carried out as per ICH-Guidelines (Q1A) at 25±2ºC/60±5% RH and 40±2ºC/75±5% RH. For every 45days the parameters like physical appearance, weight variation, hardness, friability, drug content ,*in-vitro* release studies and in-vitro permeation studies were determined.

RESULTS AND DISCUSSION

In the present study, an attempt was made to develop medicated lollipop of albendazole. Formulations were subjected to various parameters such as weight variation, thickness, diameter, hardness, drug content, friability, *in-vitro* dissolution study, *in-vitro* permeation study. Stability studies were performed as per ICH-Guidelines (Q1A). Figure 1 and Figure 2 shows the FT-IR spectra of pure drug and excipient which showed that there is no interaction found between drug and excipient. All the formulations showed good physical appearance. The weight variation was found to be in range of 4.98±0.01gm to4.99±0.09gm. Thickness was found to be in the range of

8.45±0.01mm to 8.50±0.05mm. The results of weight variation and thickness were depicted in Table2.

Table 2. Evaluation Parameters of Medicated Lollipop of Albendazole

Parameters	F0	F1	F2	F3	F4
Weight variation(gm)	4.98±0.01	4.98±0.02	4.98±0.01	4.98±0.05	4.99±0.09
Thickness(mm)	8.50±0.05	8.46±0.09	8.48±0.03	8.45±0.01	8.49±0.07
Hardness(kg/cm^2)	7.40±0.05	7.47±0.09	7.41±0.15	7.52±0.19	7.51±0.17
% Friability	0.42	0.44	0.48	0.38	0.46
% Drug content	81±0.577	85.6±0.769	92±0.192	96±0.962	87±0.384

Hardness was found to be in the range of 7.40±0.05kg/cm^2 to 7.52±0.19kg/cm^2 whereas the percentage friability was found to be in range of 0.38% to 0.48% which was found to be well within maximum 1% limit. The results of hardness and friability indicated that the lollipops are mechanically stable. The drug content was found to be in range of 81±0.577% to 96±0.962% which is within acceptable range as specified in Indian Pharmacopoeia. The results of hardness, friability and drug content showed in Table 2.

The *in-vitro* dissolution study of formulation F0 (without polymer) was found to be 80.39% at 30min. Individual formulations F1and F2 (containing methyl cellulose) showed the percentage cumulative drug release of 87.27% at 30min and 80.90% at 30 min respectively, The formulation F3and F4 (containing HPMC K4M) showed the percentage cumulative drug release of 93.51% at 30min and 90.27% at 30 min respectively. The details of *in-vitro* dissolution studies (Paddle method) showed in Table 3.

The *in-vitro* dissolution study of formulation F0 (without polymer) was found to be 80.8% at 30min. Individual formulations F1and F2 (containing methyl cellulose) showed the percentage cumulative drug release of 70.1% at 30min and 73.4% at 30 min respectively, The formulation F3and F4 (containing Hydroxypropylmethylcellulose K4M) showed the percentage cumulative drug release of 84.3% at 30min and 72.7% at 30 min respectively. The details of *in-vitro* dissolution studies (Flow through method) showed in Table 4.

The *in-vitro* permeation study of formulation F0 (without polymer) was found to be 61.3% at 30min. Individual formulations F1and F2 (containing methyl cellulose) showed the percentage cumulative drug release of 66.3 % at 30min and 60.7 % at 30 min respectively, The formulation F3and F4 (containing Hydroxypropylmethylcellulose K4M) showed the percentage cumulative drug release of 72.2 % at 30min and 63.7 % at 30 min respectively. The details of *in-vitro* permeation study showed in Table 5.

The stability studies were carried out for F3 formulation at 25±2ºC/60±5% RH and 40±2ºC/75±5% RH for two month. The results indicated that the lollipops did not show any physical changes (weight variation, thickness, hardness and friability) during the study period and the drug content was found at the end of two month. The details of Physico-chemical characterization of formulation during stability studies showed in Table 6(a) and (b).There were no significant differences found in the percentage cumulative drug release after stability studies. The details of *in-vitro* dissolution studies of formulation during stability studies showed in Table 7 and 8. There were no significant differences found in the in-vitro permeation drug release after stability studies. The details *of in-vitro* permeation studies of formulation during stability studies showed in Table 9. The stability studies showed very slight changes in dissolution and *in-vitro* permeation studies. Figure 3 and 4 shows the comparison of drug release profile of all formulations. Figure 5 shows the comparison of *in-vitro* permeation study of all formulations. This indicates that lollipops are fairly stable at storage condition. Hydroxypropylmethylcellulose K4M is a hydrophilic polymer, hence facilitates quick release of drug. But as the concentration crosses the optimum quantity it retards drug release.

Table 3. *In-vitro* drug release data of formulation F0 to F4(Paddle method)

Time (min)	F0	F1	F2	F3	F4
5	22.4	26.9	19.6	32.3	27.6
10	36.9	42.3	33.8	48.3	43.9
15	50.3	55.4	48.7	62.9	57.8
20	63.2	68.9	61.9	75.6	71.7
25	75.8	80.3	73.6	87.3	83.9
30	80.3	87.2	80.9	93.5	90.2

Table 4. *In-vitro* drug release data of formulation F0 to F4 (Flow through method)

Time(min)	F0	F1	F2	F3	F4
5	24.8	23.7	24.3	26.3	21.9
10	44.6	39.7	43.8	46.3	38.6
15	61.7	53.7	60.7	63.9	52.7
20	74.2	61.7	67.7	76.3	61.9
25	78.1	66.8	70.8	81.7	69.4
30	80.8	70.1	73.4	84.3	72.7

Table 5. *In-vitro* permeation study data of formulation F0 to F4

Time(min)	F0	F1	F2	F3	F4
5	14.2	16.4	13.9	21.9	20.3
10	26.3	29.4	25.7	34.6	32.4
15	36.7	40.3	35.3	47.2	45.1
20	46.2	50.1	45.3	60.1	57.4
25	55.8	58.9	54.9	68.8	64.9
30	61.3	66.3	60.7	72.2	67.3

Table 6. (a) and (b) Physico-chemical characterization of formulation during stability studies

Time days		Weight variation (gm)	Thickness (mm)
		F3	F3
0		4.98	8.45
30	At 25±2˚C/60±5% RH	4.98	8.44
	At 40±2˚C/75±5%RH	4.78	8.38
60	AT 25±2˚C/60±5%RH	4.96	8.42
	AT 40±2˚C/75±5%RH	4.76	8.36

Time days		Hardness (kg/cm)	Friability (%)	Drug content (%)
		F3	F3	F3
0		7.52	0.38	96
30	At 25±2˚C/60±5%RH	7.51	0.39	92.7
	At 40±2˚C/75±5%RH	7.49	0.40	96.9
60	AT 25±2˚C/60±5%RH	7.49	0.39	95.3
	AT 40±2˚C/75±5%RH	7.47	0.41	96.0

Table 7. *In-vitro* drug release data of medicated lollipops of Albendazole formulations after stability studies (Paddle method)

Formulation	Cumulative drug release (%) at time 30 min				
	At 0 day	At 30 day		After 60 day	
	-	A *	B**	A *	B **
F3	92.51	91.86	89.67	91.85	89.65

A *:25±2˚C and 60±5%RH, B:40±2˚C and 75±5%RH**

Table 8. *In-vitro* drug release data of medicated lollipops of Albendazole formulations after stability studies (Flow through method)

Formulation	Cumulative drug release (%) at time 30 min				
	At 0 day	At 30 day		After 60 day	
	-	A *	B**	A *	B **
F3	83.34	82.46	80.32	82.36	80.24

A *:25±2˚C and 60±5%RH, B:40±2˚C and 75±5%RH**

Table 9. *In-vitro* permeation data of medicated lollipops of Albendazole formulations after stability studies

Formulation	Cumulative drug release (%) at time 30 min				
	At 0 day	At 30 day		After 60 day	
	-	A *	B**	A *	B **
F3	71.40	70.47	68.32	70.42	68.26

A *:25±2˚C and 60±5%RH, B:40±2˚C and 75±5%R**

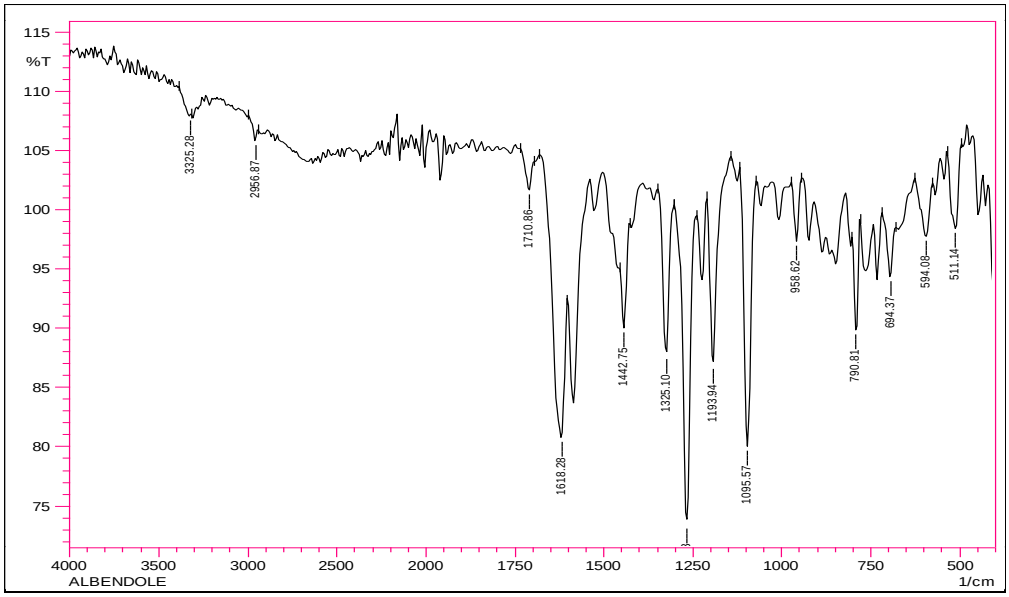

Figure 1: FTIR spectra of Albendazole

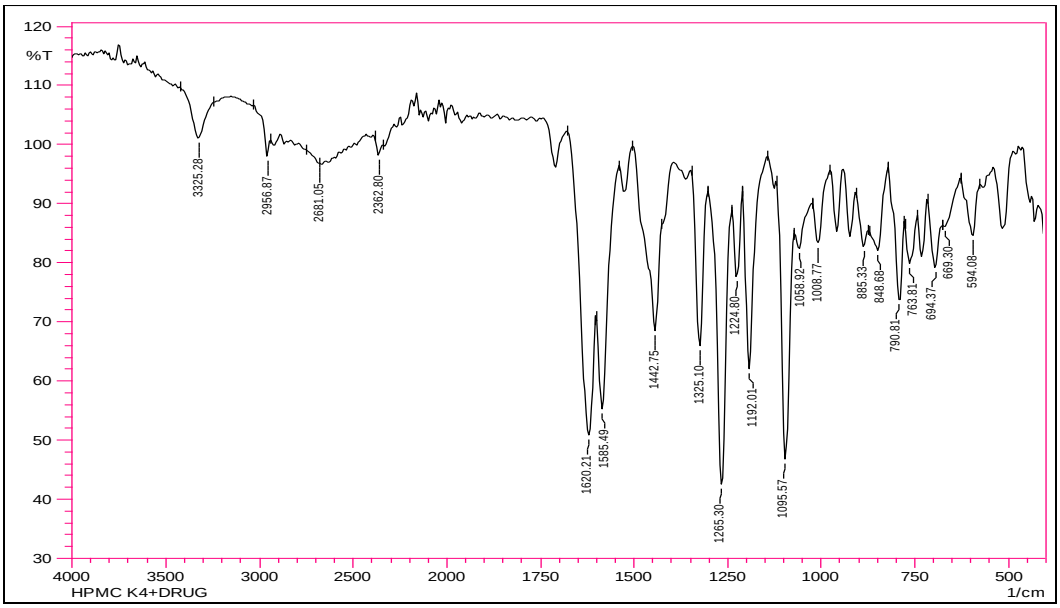

Figure 2: FTIR spectra of Albendazole+HPMC K4M

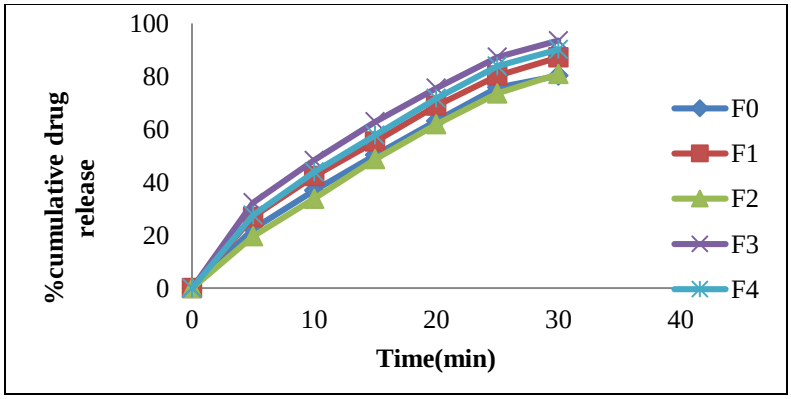

Figure 3: *In-vitro* release study data of formulation F0 toF4 (Paddle method)

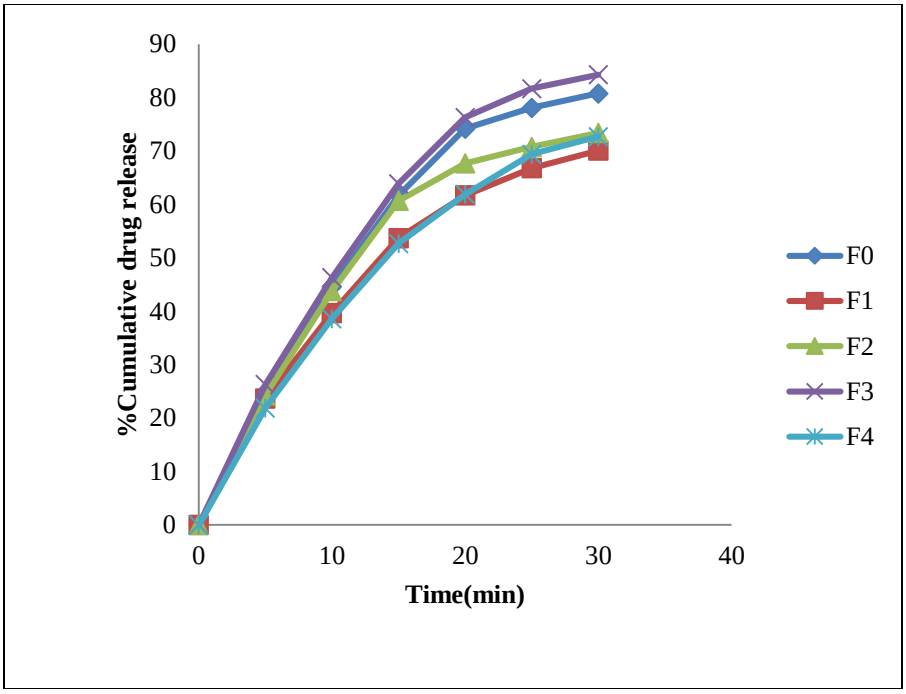

Figure 4: In-vitro release study data of formulation F0 toF4 (Flow through method)

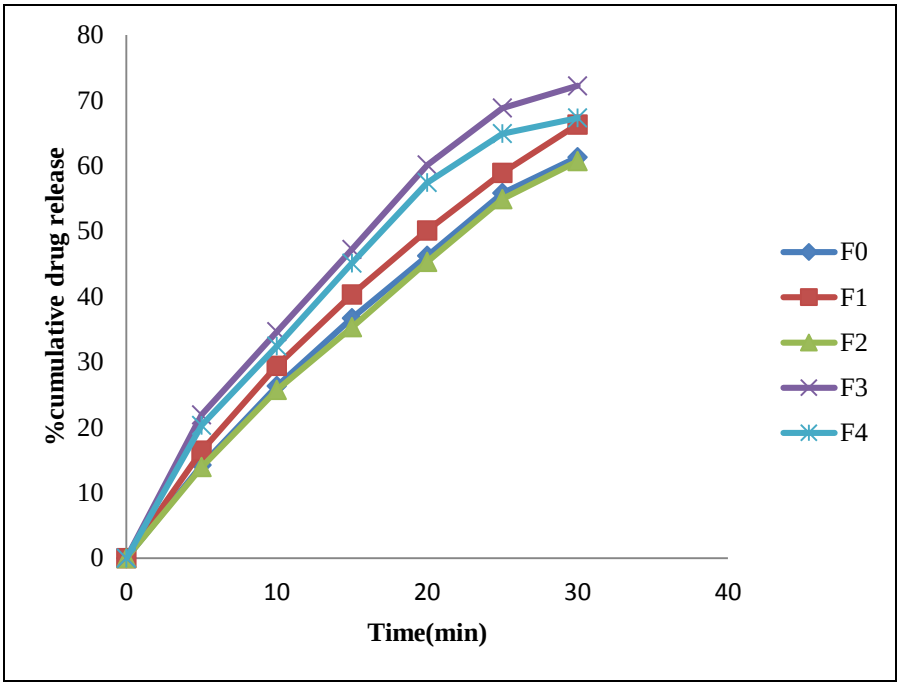

Figure 5: In-vitro permeation study data of formulation F0 toF4

CONCLUSION

From the above investigation it is concluded that incorporating polymer like Hydroxypropylmethylcellulose K4M can be used to formulate effective medicated lollipop. This will offer better patient compliance and innovative dosage form. Hence, it leads to extended release formulation and increase the oral retention time of medicated lollipop.

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