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FORMULATION AND EVALUATION OF ANTIEMETIC DRUG LOADED LOLLIPOP FOR PAEDIATRIC USE

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ABSTRACT

The medicated lollipops are flavoured mediated dosage forms which are intended to be sucked or held on the mouth or pharynx containing one or more medicaments usually in a sweetened base. The Antiemetic lollipop (AEL) prepared with DOM is a good and attractive formulation for the paediatric use. It is very effective during travelling for those who have motion sickness and also for other conditions. To improve the bioavailability, the drug was made as QIC with βCD, CA and mannitol in two different ways named physical mixture and kneaded complex. Out of this, KC with equimolar concentration of DM, βCD, CA and mannitol is found to be highly water soluble than the other complexes. This is why because of the conversion of the crystalline character of the DM to amorphous through the formation of QIC and its confirmed through solubility, FTIR, PXRD studies. This QIC is used for the development of AEL. Ten formulations were prepared using different concentrations of excipients. F1 was formulated with DM and the F2-F10 with QIC. All formulations were evaluated through different parameters and finally found that F9 prepared with methyl cellulose and glycerine as polymer and plasticizer respectively provides the best result of assay, *in vitro* dissolution and other parameters also provide good result. Hence F9 is found to be the optimum formulation and it was further used for the stability studies. Finally after the completion of the stability study it was concluded that the optimum formulation of AEL is sterile and stable over shelf life.

Keywords: Antiemetic lollipop; Domperidone maleate; βCyclodextrine; Quaternary inclusion complex

INTRODUCTION

Vomiting is one of the common conditions that affect most of the people. Most commonly it happens during travelling and is called as motion sickness. Antiemetic medicaments are available for the treatment of such problems. There are different types of conventional dosage forms are available for the formulation of antiemetic drugs like tablets, syrups etc. The administration of drugs through oral route is the most common and the easiest way **[1]**. Conventional oral solid dosage forms will be defined as those solid dosage forms taken by or given orally to patients and intended to deliver the drug to the site of action without any delay in time.

Lollipops are flavored medicated dosage form intended to be sucked and held in the mouth or pharynx containing one or more medicam-ents usually in the sweetened base. Lollipops are large sugar boiled confectionary of various flavors attached to a plastic stick which can be consumed over a long period of time through licking. The plastic stick is used to hold the confection together **[2]**. Medicated lollipop is designed to improve the patient compliance and acceptability. It containing medicament in a sweetened flavored base, indented to dissolve slowly in the mouth. Lollipops are mainly contained sweetening agent, flavoring agent, coloring agent, opacifiers and stabilizing agents **[3]**. Lollipop is used for patients who cannot swallow solid oral dosage forms as well as for medications designed to be released slowly to yield a constant level of drug in the oral cavity or to bathe the throat tissues in a solution of the drugs often incorporated into lollipop include analgesics, anesthetics, antimicrobials, antiemetics, antidepressants, antiseptics, antitussives, aromatics, astringents, corticosteroids, decongestants, and demulcents. However, this is by no means an exhaustive list as many other drugs may lend themselves to delivery by a lollipop **[4]**.

Antiemetic drugs are used to prevent or suppress vomiting**.** Number of antiemetic drugs are available for the treatment of nausea and vomiting and are used for specific conditions. Domperidone maleate (DOM) is a D_2 receptor antagonist drug often used to treat vomiting due to cytotoxic therapy as well as gastrointestinal symptoms **[5]**. Unlike metoclopramide, it does not readily penetrate the blood–brain barrier and is consequently less prone to producing central side effects. Both drugs are given orally, have plasma half-lives of 4–5 h and are excreted in the urine **[6]**.

Since Domperidone maleate is a poorly water soluble drug, its absorption from the oral cavity through sublingual route is very limited. To improve this characteristics the Domperidone maleate is converted into its

Quaternary inclusion complex by using β cyclodextrin. This QIC of DOM is then included in the lollipop as a drug source **[7]**.

MATERIALS AND METHODS

Domperidone maleate was collected from Balaji drugs and chemicals, Nashik, Maharashtra. Research lab, Mumbai provided β cyclodextrin and methyl cellulose. HPMC required for this study was supplied by Yarrow chem, Mumbai. Citric acid, sucrose and dextrose were collected from Vikash Pharma, Sisco Research Laboratories and Molychem respectively. All other materials were provided by Nice Chemicals, Cochi.

Preparation of QIC

1. Preparation of Physical Mixtures (PM)

DM, βCD, and CA were weighed in an equimolar ratio (1:1:1) whereas the amount of mannitol was varied in different molar ratios (0.25, 0.5, and 1) with respect to other components. The weighed components were mixed and were pulverized using mortar and pestle followed by sifting through 100μm mesh **[8, 9]**.

2. Preparation of Kneaded Complex (KC)

The QICs of DM, βCD, CA, and mannitol, in the same molar ratio to that of PMs, were prepared by kneading method. Accurately weighed quantity of βCD was mixed with sufficient quantity of water to obtain a smooth and homogeneous paste. Weighed quantity of DM along with CA and mannitol was added slowly by grinding. The mixture was ground for 30 min. Finally, the paste was dried in hot air oven at 40°C until it gets dried. The dried complex was powdered and passed through 100μm mesh and stored in airtight glass desiccators under vacuum till further use.

Evaluation of QIC

1. Drug Content estimation

QICs equivalent to 10 mg of DM was accurately weighed and added into 100 ml volumetric flask and then 50 ml of artificial saliva was added to it. The resultant solution was stirred for 60 min, till the entire drug leached out. This solution was suitably diluted with distilled water, shakes well and filtered. From this 1ml of the solution was pipetted and made up to 10ml with distilled water. Drug content was estimated spectrophotometrically at 284 nm using distilled water as blank. The same procedure was followed to determine the drug content in the physical mixtures and other kneaded complexes **[8]**.

2. Saturation Solubility Study [8, 10]

Saturation solubility studies were conducted for the physical mixtures, kneaded complexes, and the DM in distilled water according to the method reported by Higuchi and Connors. Excesses of DM, physical mixtures, and kneaded complexes were added to 10 ml distilled water taken in standard flask. The standard flasks were kept at room temperature for 48hr with occasional stirring. After the complete

equilibration, the supernatant solutions were collected carefully and filtered using whatmann filter paper no 1. The filterate was collected and appropriately diluted and the concentration of DOM was determined using UV-visible spectrophoto- meter at 284 nm **[8, 10]**.

3. FT – IR Spectroscopy

Integrity of the complex was checked by taking an IR spectrum of the selected complex along with the drug and other excipients. The spectra were taken by using Shimadzu IR prestige-21 spectrophotometer and were compared with standard spectra. The FT-IR spectra were as shown in **Figure 1 [11]**.

4. Powder X- Ray Diffraction

The sample was taken on the specially designed sample holder and kept it on the sophisticated PXRD equipment and allow it to run. The X- Rays from the source strikes on the material at specific angle and the reflected rays were collected at the receiver. This data was decoded using computer and the peaks and its intensity were obtained from the computer. The PXRD data were shown on the **Figure 5 and 6**.

Formulation of Antiemetic lollipop (AEL)

Required quantity of sugar syrup was prepared by mixing sugar and water. Dextrose was dissolved in small quantity of water and heated it to 110^0C till dextrose dissolves completely forming clear viscous syrup. Then the dextrose syrup was poured into the sugar syrup and heated to 160^0C until the colour changes to golden yellow. Colour was added in 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 into the calibrated mould and kept it for air dry for 1-2 hr. The prepared lollipops were wrapped with plastic cover and stored in desiccators to prevent moisture uptake **[1]**.

Table 1: Formulation of antiemetic lollipop

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
DM (mg)	6.5	----	----	----	----	----	----	----	----	----
QIC (mg)	----	150	150	150	150	150	150	150	150	150
Sucrose (mg)	3000	3000	3000	3000	3000	3000	3000	3000	3000	3000
Dextrose (mg)	1468.5	1325	1300	1275	1325	1300	1275	1300	1300	1300
Methyl Cellulose (mg)	25	25	50	75	----	----	----	50	50	50
HPMC (mg)	----	----	----	----	25	50	75	----	----	----
PEG (%)	1	1	1	1	1	1	1	----	----	----
Glycerine (%)	----	----	----	----	----	----	----	1	3	5
Colouring agent	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

Evaluation of AEL

1. General Appearance

The general appearance of the lollipop was evaluated through visual observation. The color, odor, taste and shape should be uniform. The results were tabulated in **Table 6**.

2. Weight Variation

10 Lollipops were weighed individually; its average weight and percentage weight variation were calculated. The requirements are met if the weights of not more than 2 of the Lollipops differ from the average weight by more than the percentage listed in the accompanying table and no lollipops differs in weight by more than double that percentage. The results were tabulated in **Table 6 [2, 12]**.

$$\% \text{ Variation} = \frac{\text{Average wt.} - \text{Individual wt.}}{\text{Average wt.}} \times 100$$

3. Hardness

The force required to break the lollipop is measured in terms of kilograms. by using Pfizer hardness tester and about 4Kg/cm^2 is considered as the minimum. Hardness above 4Kg/cm^2 is considered as good formulations. The results were tabulated in **Table 6 [1, 12]**.

4. Thickness

Thickness of the lollipop is measured for the convenience of packaging. The thickness should be controlled to within ±5% of an established standard value. The thickness can be measured using vernier caliper. The results were tabulated in **Table 6 [1, 12]**.

5. Friability

10 lollipops were weighed accurately and placed in the Rosche friabilator and was for 4 minutes. The lollipop is then de dusted and weighed. The weight loss of 0.5 to 1% is considered as acceptable limits. The results were tabulated in **Table 6 [1,12]**.

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

6. Assay

Preparation of artificial saliva

About 0.844gm of Sodium Chloride, 1.2g of Potassium Chloride, 0.193g of Calcium Chloride dihydrate, 0.111g of Magnesium Chloride hexahydrate and 0.342g of Potassium Phosphate dibasic were dissolved in 500ml of distilled water. After the complete dissolution of powder, volume was made up to 1000ml with distilled water. The pH was adjusted with 0.1N hydrochloric acid to 6.8 **[13, 14]**.

Preparation of sample solution

For the estimation in dosage form, 5 lollipops were weighed and powdered. Amount equivalent to 12.7 mg of DM from powdered formulation was accurately weighed and taken in 100ml volumetric flask, added small quantity of artificial saliva and sonicated for 20 minutes. Cool the solution to room temperature and make up the volume with artificial saliva. Filtered the

solution, from the filtrate 1ml was pipetted into 10ml standard flask and made up the volume and measure the absorbance at 284nm. The results were shown in **Table 6 [2, 4]**.

7. *In- vitro* Dissolution

In vitro release studies were performed using USP Apparatus II (Paddle type). The dissolution test was performed using 900 ml of artificial saliva, 37 ± 0.5°C, 50 rpm. 10ml of samples were withdrawn at predetermined time intervals. The samples analyzed directly without any dilution using UV-Visible spectrophotometer at 284 nm. The results were tabulated in **Table 6 [1, 4]**.

8. Kinetics of *In- Vitro* Drug Release

There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and reference dissolution profiles zero order, first order, Higuchi model and Korsmeyer - Peppas model **[15, 16]**.

9. Accelerated Stability Study

As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C±2˚C / 75±5% RH for a period of 3months. The samples were analyzed at 0, 2 and 3 month's time points **[17, 18]**.

RESULTS AND DISCUSSIONS

Evaluation of QIC

1. Drug Content Estimation

The total drug content of both PM and KC were found and the results from all mixtures were above 90%. This indicates the minimal drug loss and maximum yield of product **(Table 2)**.

2. Saturation Solubility

The solubility of DM, its PM and KC were evaluated, the results were tabulated in **Table 3**. The solubility of DOM in water was increased tremendously in both PM and KC form. Out of this KC3 is much better than PM's and other KC's.

3. FT-IR

FT-IR study of QIC was carried out to confirm the changes that happened in the DM due to complexation with βCD **(Figure 1)**.

The intensity of C=O and C-H stretching peaks of DM get reduced due to the complexation with βCD. There is a slight shift in the position of C-N stretching peak due to the weak intermolecular reaction with βCD, CA or mannitol. On the other side, peak resulting due to N-H stretching disappeared. In the spectrum of QIC, there is a peak at 1030.77cm^{-1} due to C-O stretching of mannitol. This indicates the interaction of mannitol with other components and formation of a co-complex. Reduction in intensity or disappearance of the peaks indicates the DM- βCD interaction and amorphization of the product.

4. PXRD

The crystallinity of DM makes it poorly water soluble. The QIC prepared with βCD, CA and mannitol in equimolar concentration

provides the best water solubility results. Hence its PXRD were analyzed and the graph was shown below. It was found that the intensity of the peaks of DM was reduced due to the amorphization of QIC **(Figure 2)**.

EVALUATION OF AEL

1. General Appearance (Table 5)

2. Evaluations

The results of various evaluations carried out on the AEL were tabulated in **Table 6**. The invitro dissolution profile of the AEL is given below **(Figure 4 & 5)**.

3. Kinetics of Drug Release

The *in vitro* drug release data was obtained from the dissolution study and those data were subjected to goodness of fit by linear regression analysis, according to zero order, first order kinetic equation, Higuchi and Korsmeyer models to ascertain the mechanism of drug release and it was found that formulation strictly follows first order kinetics **(Figure 5-8)**.

4. Accelerated Stability Studies

Accelerated stability studies were carried out on the optimized formulation (F9) for 3 months. The changes that happened on the formulation were studied through comparing the parameters before and after the stability testing and the comparison were given on the **Table 7**. Dissolution profile of F9 before and after stability studies were shown in **Table 8**.

Table 2: Drug content estimation of QIC

Sl. No.	System	Molar Ratio	Drug Content (%)
1	DM: βCD: CA: Mannitol (PM1)	1:1:1:0.25	90.7±0.13
2	DM: βCD: CA: Mannitol (PM2)	1:1:1:0.50	96.2±0.19
3	DM: βCD: CA: Mannitol (PM3)	1:1:1:1	97.1±0.09
4	DM: βCD: CA: Mannitol (KC1)	1:1:1:0.25	91.5±0.22
5	DM: βCD: CA: Mannitol (KC2)	1:1:1:0.50	97.4±0.20
6	DM: βCD: CA: Mannitol (KC3)	1:1:1:1	98.3±0.24

Table 3: Study of Solubility of QIC

Sl. No.	System	Molar Ratio	Solubility in Water at 25^0C (mg/ml)
1	DM	1	10.04±0.7
2	DM: βCD: CA: Mannitol (PM1)	1:1:1:0.25	95.35±1.74
3	DM: βCD: CA: Mannitol (PM2)	1:1:1:0.50	129.57±1.60
4	DM: βCD: CA: Mannitol (PM3)	1:1:1:1	161.79±1.24
5	DM: βCD: CA: Mannitol (KC1)	1:1:1:0.25	574.75±1.03
6	DM: βCD: CA: Mannitol (KC2)	1:1:1:0.50	621.26±1.28
7	DM: βCD: CA: Mannitol (KC3)	1:1:1:1	704.64±1.42

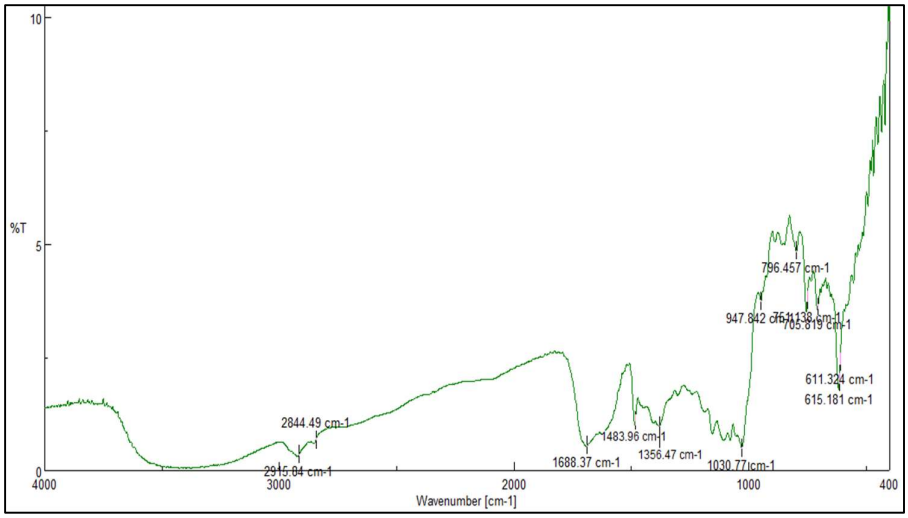

Figure 1: FT-IR Spectrum of QIC

Table 4: IR Intepretation of QIC

Functional group and Vibration	Characteristic wave number	observed wave number
C=O Stretching	1900-1600 cm^{-1}	1688.37 cm^{-1}
C-H Stretching	2960-1590 cm^{-1}	2915.84 cm^{-1}
C-N Stretching	1342-1266 cm^{-1}	1356.47 cm^{-1}

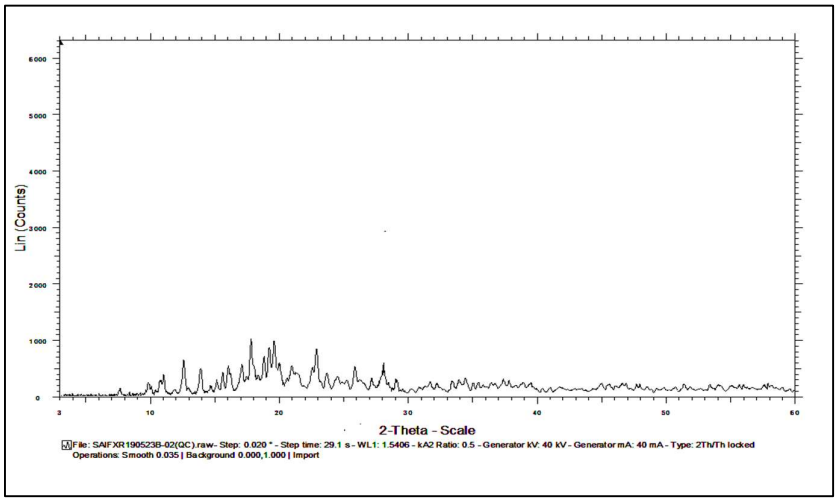

Figure 2: PXRD image of QIC

Table 5: General morphological evaluations of AEL

Sl. No.	Test	Specifications	Result
1	Colour	Orange to Red	Complies
2	Odour	Caramel	Complies
3	Taste	Sweet	Complies
4	Shape	Flower	Complies
5	Total appearance	Attractive	Attractive

Table 6: Evaluation of AEL

Formulation	Average weight (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)	Percentage drug release (at 30 min)
F1	4545±5.85	10.37±0.21	6.32±0.07	0.08±0.001	87.43±0.48	72.08±0.52
F2	4483±6.61	10.11±0.19	6.09±0.10	0.09±0.001	94.82±0.51	92.16±0.32
F3	4537±6.07	11.24±0.25	6.27±0.06	0.08±0.001	99.06±0.16	97.82±0.14
F4	4498±7.17	10.58±0.20	6.20±0.11	0.10±0.002	97.77±0.94	95.25±0.07
F5	4532±6.28	10.44±0.15	6.35±0.05	0.06±0.001	94.29±0.78	89.59±1.15
F6	4516±5.55	10.36±0.21	5.97±0.03	0.09±0.002	98.86±0.22	96.29±0.07
F7	4532±5.94	10.40±0.26	6.18±0.09	0.06±0.002	98.55±0.72	94.22±0.08
F8	4525±6.24	10.39±0.18	6.25±0.09	0.07±0.001	99.13±0.20	97.82±0.06
F9	4511±6.11	10.21±0.16	6.22±0.07	0.05±0.002	99.64±0.19	98.85±0.03
F10	4509±7.26	10.82±0.22	6.16±0.09	0.09±0.001	98.94±0.24	96.29±0.05

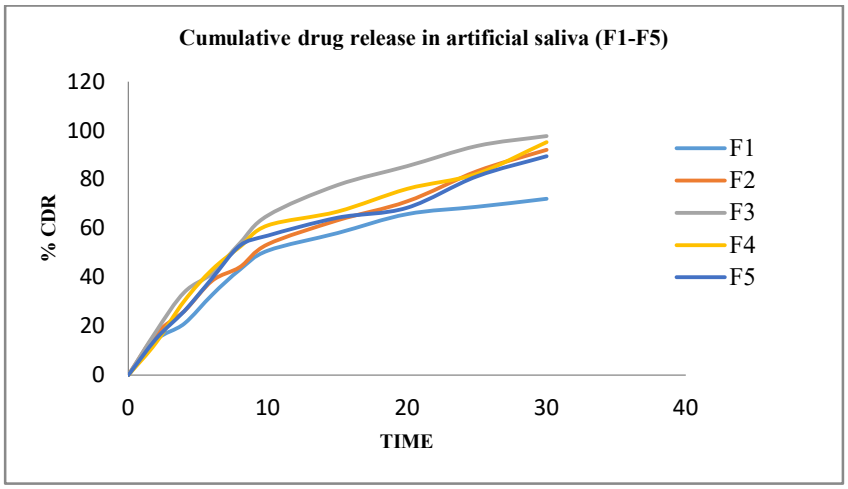

Figure 3: Drug release profile of F1-F5 formulations

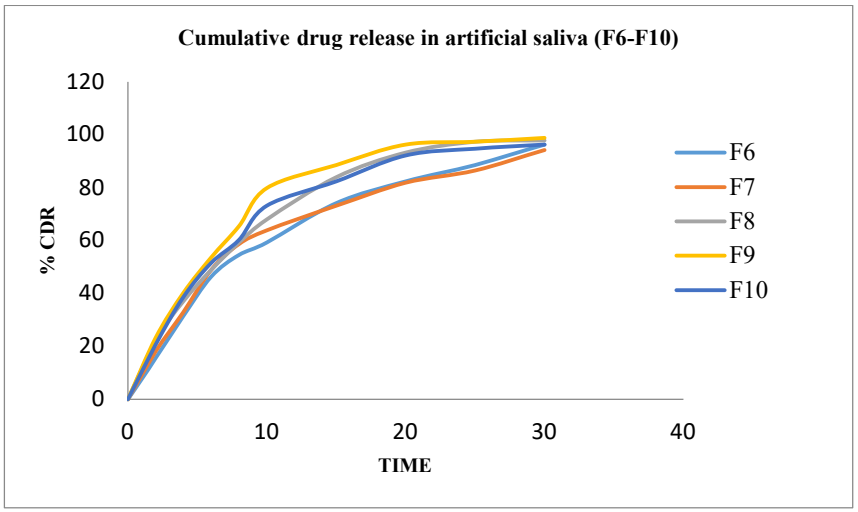

Figure 4: Drug release profile of F6-F10 formulations

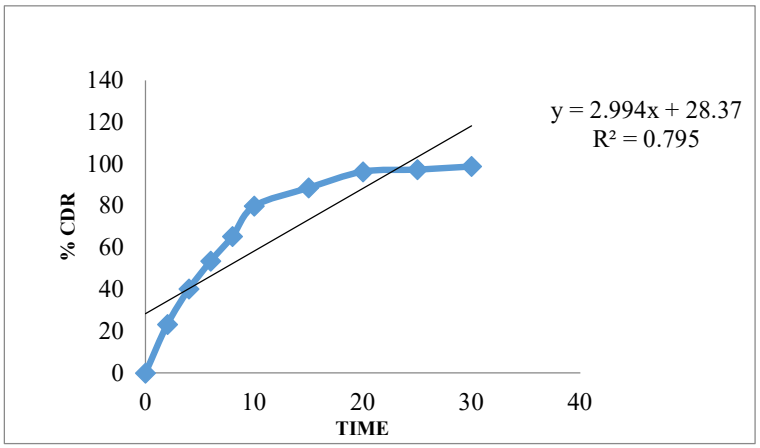

Figure 5: Zero order drug release profile of F9

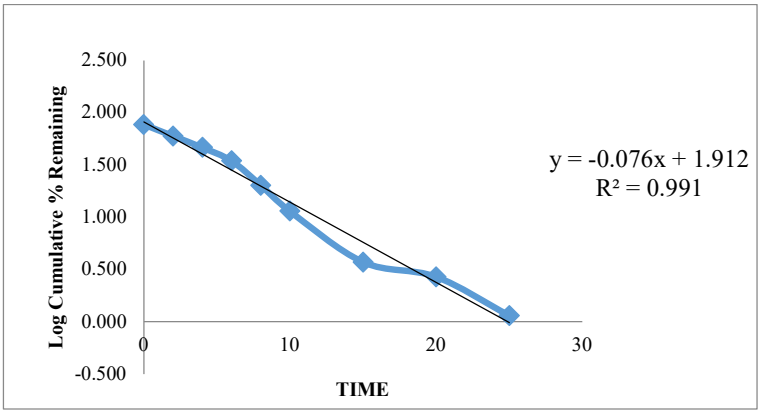

Figure 6: First order drug release profile of F9

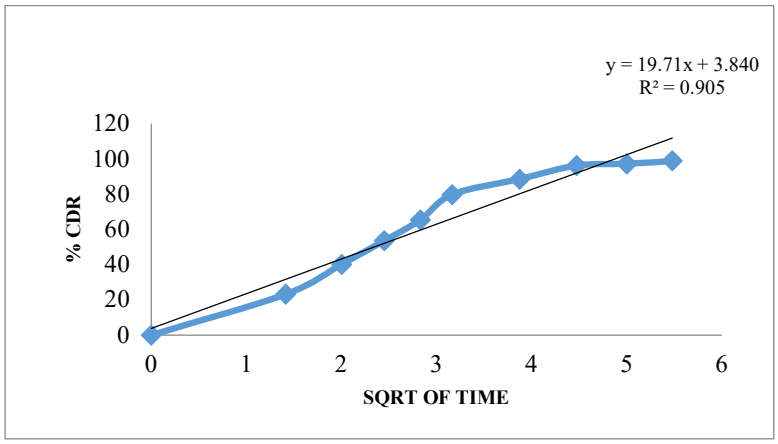

Figure 7: Higuchi model drug release profile of F9

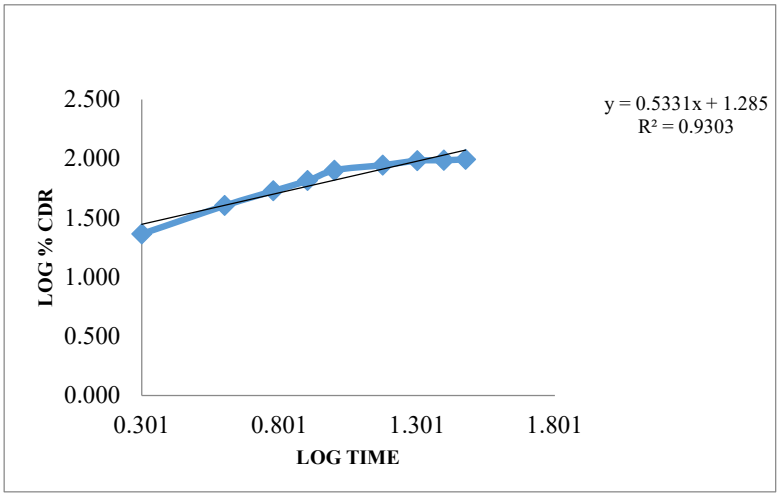

Figure 8: Korsmeyer – Peppas model drug release profile of F9

Table 7: Evaluation of AEL after accelerated stability studies

Parameters	Before stability studies (F9)	Stability study after two month (F9)	Stability study after three month (F9)
Description	Red coloured flower shaped, caramel flavoured lollipop	No characteristic changes	No characteristic changes
Hardness (Kg/cm^2)	10.63	10.61	10.60
Drug content	99.61%	99.60%	99.59%
Antimicrobial study	Negative	Negative	Negative

Table 8: Evaluation of drug release profile after accelerated stability studies

Time (min)	Before stability studies (F9) % CDR	Stability study after two month (F9) % CDR	Stability study after three month (F9) % CDR
2	23.31	23.05	22.79
4	40.26	38.77	38.02
6	52.73	52.36	52.04
8	65.96	65.24	64.18
10	78.05	77.87	77.45
15	88.29	88.05	87.60
20	96.85	96.78	96.22
25	97.39	97.33	97.30
30	98.86	98.85	98.83

CONCLUSION

The character of DM was found through preformulation studies like morphological evaluations, solubility, melting point, loss on drying etc. and it complies with the standard. DM is a drug which has a poor bioavailability and bitter taste. The major reason for its poor bioavailability is its low water solubility. The crystal habit of DM is the reason for difficulty in water solubility. Hence the crystalline nature of DM is converted into amorphous through QIC preparation with βCD, CA and mannitol. The formation of QIC was confirmed through its saturation solubility study, PXRD and the drug content of complexes were estimated, which was found to be good. QIC prepared with KC using equimolar concentration of components provides the best result than the PM. The

data clearly shows that the crystalline character of DM was changed. This resulted in drastic change to its water solubility. Hence the first barrier was rectified.

The next difficulty is its bitter taste and improvement of patient adherence. The medicated lollipop is a good alternative. Hence the prepared QIC is incorporated in the lollipop. The lollipop was formulated through H&C method. Paediatric dose for DM is about 5mg for single dose. Hence all formulation contains 5mg of DM. MC and HPMC were used as polymers and PEG and Glycerine were used as plasticizers at different concentrations. Ten formulations were prepared with these ingredients at different concentrations. Out of that F1 was formulated with pure DM to compare the difference. All formulations were evaluated with different parameters hardness, thickness, weight variations, *in vitro* dissolution, microbial resistance etc. The percentage drug content and percentage drug released from F1 was very low when compared to other formulations because it was formulated with DM while all other formulations have above 90% of drug content and drug release. Out of this the best result was provided by F9 and its percentage drug content and drug release were 99.64% and 98.85% respectively. F9 also has better results for other parameters. Hence it was concluded that F9 as the best formulation and was subjected to stability study. After completion of the stability studies it was found that it has a better stability over time.

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