Design and evaluation of Carbamazepine lozenzes

Abstract:

Lozenges are the flavoured solid, unit dosage medicated dosage formsusually in the sweetened base intended to be sucked and held in the mouth or pharynx containing one or more medicaments. Lozenges were developed in 20th century and is still under commercial production. These are medicated confections designed for local as well as systemic therapy.

Carbamazepine (CBZ) is an anticonvulsant drug used in the treatment of epilepsy and neuropathic pain. It is used in schizophrenia along with other medications.

In the present study an attempt has been made to prepare and evaluate the sugar based medicated Carbamazepine lozenzes to improve bioavailability and increase patient compliance specially for those patients who have difficulty in swallowing. The lozenges were prepared using sucrose as base; HPMC K4M, methyl cellulose were used as polymers. Eudragit was used as taste masking agent. Formulations were prepared by heating and congealing method on laboratory scale

All the formulations prepared were subjected to variousphysicochemical parameters like hardness, friability, weight variation, drug content and in vitro dissolution studies.

Stability studies of selected formulations of batch CL4 were also carried out at 40/75% relative humidity for 6 months for a period of six months. There wasn't any substantial interaction between the drugs, flavor and color and other parameters and the prepared formulations were found to be stable.

Keywords: Lozenges, HPMC K4M, Carbamazepine (CBZ), swallowing, in vitro dissolution, stability studies.

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Introduction

The word "Lozenge" is derived from French word "Losenge" which indicates a diamond shaped geometry with four equal sides[1]. Lozenges are the flavouredmedicated solid, unit dosage forms intended to be sucked and held in the mouth or pharynx containing one or more medicaments usually in the sweetened base[2]. They dissolve slowly in the mouth and so release the drug dissolved in the saliva. The drugs having a large dose can be easily administered formulating as lozenges. The oral route of drug administration is most preferred route because of many advantages associated with it like ease of ingestion, pain avoidance, versatility and most important patient compliance[3]. However geriatric and pediatric patients suffer from dysphagia (difficulty in swallowing), thus oral route for drug administration is not suitable in these cases. There are other conditions in which oral route is not preferred like unavailability of water, sudden episodes of allergic attack, mentally retarded patients[4].

Most of the lozenge preparations are available as over the counter medications. The dosage form can be adopted for local as well as systemic therapy and a wide range of drugs like analgesics, anesthetics, antimicrobials, antiseptics, antitussives, aromatics,astringents, corticosteroids, decongestants, demulcents and other can be delivered in the form of lozenges[5]. Lozenges are associated with many advantages like avoidance of first pass hepatic metabolism, no need of water intake, reduction in gastric irritation, improved bioavailability with reduced dosing frequency to minimum side effects[6].

Carbamazepine (CBZ) is an anticonvulsant is a medication used primarily in the treatment of epilepsy and neuropathic pain[7]. It is used in schizophrenia along with other medications and as a

second line agent in bipolar disorder. Carbamazepine is relatively slowly but well absorbed after oral administration[8,9].

In present study lozenges of Carbamazepine were prepared in order to improve bioavailability and increase patient compliance.

Materials and methods

Carbamazepine was obtained from Reals Pharmaceuticals Limited, Lagos, Nigeria. Eudragit E 100 , methyl cellulose, Polyethylene glycol 8000 and HPMC K4M wereobtained from AC drugs ltd (Enugu, Nigeria). Sucrose and dextrose were provided by McNichols Plc, Ogun State, Nigeria. Citric acid was obtained from Mekz Global Limited (Lagos)

Preparation of Carbamazepine lozenges

Carbamazepine lozenges were prepared in laboratory scale by heating and congealing technique, the composition as given in table 1. Required quantity of all ingredients were transferred into a copper bowl, and then heated in a heating mantle at 150°C for 15 minutes. Then the temperature of the mixture was brought into 90°C, then Carbamazepine, polymers, flavoring agent and coloring agent were added with stirring by using glass rod, and the solutionwas transferred into a lubricated mould. It was allowed to cool for solidification thenlozenges were collected and packed in an aluminum foil[10].

Table 1: Compostion of Carbamazepine lozenges

Ingredients (mg)	Batch Code			
	CL1	CL2	CL3	CL4
Carbamazepine	10	10	10	10
Eudragit E 100	10	15	20	25
HPMC K4M	25	20	15	10
Sucrose	800	740	730	700
Dextrose	-	-	30	60
Polyethylene glycol 8000	200	250	300	350
Methylcellulose	25	20	15	10
Citric acid	30	30	30	30
Aspartame	100	100	100	100
Talc	0.0126	0.0126	0.0126	0.0126
Coloring agent	0.5	0.5	0.5	0.5
Menthol	25	25	25	25

Evaluation parameters of Carbamazepine Lozenges

1. Measurement of thickness

The thickness of Carbamazepine lozenges were determined using Vernier callipers. Three lozenges from each batch were used and average values were calculated[11].

2. Weight variation

The formulated Carbamazepine lozenges were tested for weight uniformity. Twenty formulations were collectively and individually weighed. Fromthe collective weight, average weight was calculated. Each lozenge weight was then compared with average weight to ascertain whether it is within permissible limits or not[12].

3. Hardness

The lozenge crushing strength, which is the force required to break the lozenge by compression in the diametric direction. The hardness of the Carbamazepine lozenges was determined by using

Monsanto Hardness tester, where the force required to break the lozenges was noted. It is expressed in kg/cm^2. Ten formulations of each batch were used for theestimation of hardness[13].

4. Friability:

The Roche friability test apparatus was used to determine the friability of the lozenges. Six pre weighed Carbamazepine lozenges were placed in the apparatus, for 4 min at 25 rpm. Then the lozenges were reweighed. The percentage friability was calculated by using the formula[14].

% Friability=(Initial weight-Final weight)/(Initial weight) X100

5. Drug content

Three Carbamazepine lozenges from each batch wereselected and weighed individually and crushed in a mortar. Drug was extracted with 100 ml of distilled water. The drug content was determined spectrophotometrically at 285 nm with blank lozenge extract as the reference. The formulated lozenges were evaluated for the following parameters[15].

6. In vitro dissolution studies

In vitro dissolution studies of Carbamazepine lozenges were carried out in 900 ml phosphate buffer pH6.8 using USP dissolution testing apparatus with a rotating stirrer speed at 100 rpm, and temperature of dissolution medium maintained at 37± 0.5°C. The rpmof the paddle was fixed at 100. Aliquots of 5ml were withdrawn at regular intervals; filtered and same amount of fresh dissolution medium was replaced at the same temperature. The filtered solutions were analyzed by using (Shimadzu, Japan) UV- spectrophotometer at 285 nm[16].

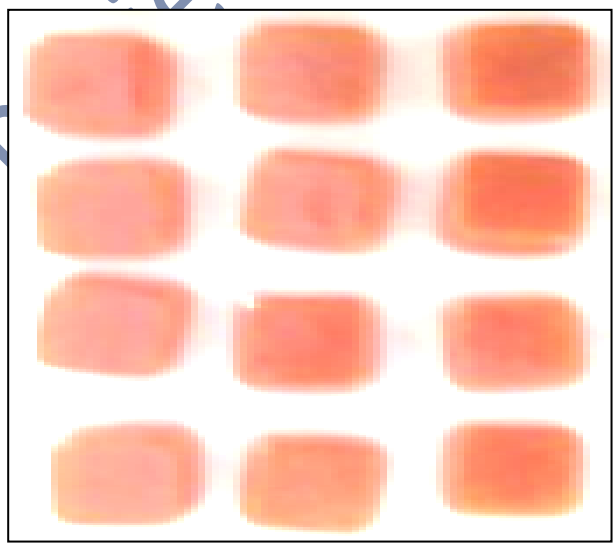
7. Disintegration test

The disintegration time of Carbamazepine lozenges were determined by USP Disintegration apparatus and disintegration time was noted in buffer of pH 6.4 at 37^{o}C[17].

8. Stability test

For accelerated stability study, selected formulation was kept in airtight darkcontainer according to ICH guidelines at 40/75% relative humidity for 6 months[18].

Results and discussion:



Physical appearance of prepared Carbamazepine lozenges

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Table 1-Evaluation parameters for Carbamzepine lozenges formulations

Batch code	Thickness (cm)	Hardness (Kg/cm^2)	% Weight variation	% Friability	% Drug content	Disintegration time (min)
CL1	14.32± 0.08	15.95± 0.13	3.25± 0.14	0.96± 0.07	96.72± 0.09	25±0.2
CL2	14.50± 0.06	16.43± 0.18	2.42± 0.07	0.93± 0.13	95.28± 0.12	24±0.1
CL3	14.38± 0.16	16.35± 0.08	4.51± 0.08	0.94± 0.25	97.47± 0.43	21±0.2
CL4	14.23± 0.12	16.47± 0.08	2.34± 0.12	0.95± 0.18	99.82± 0.52	20±0.3

Four different formulations of Carbamazepine lozenges were prepared successfully in laboratory scale by heating and congealing technique. Different ingredients i.e. Eudragit E 100, HPMC K4M, sucrose, dextrose, polyethylene glycol 8000, methylcellulose,citric acid, aspartame, talc, coloring agent, menthol were incorporated in different ratio. In the Carbamazepine lozeges formulations menthol was used as flavoring agent, it provides a desirable soothing effect.

All the formulations showed good physical appearance. The prepared tramdol hydrochloride hard lozenges evaluated for physicochemical parameters likehardness, friability, content uniformity, weight variation, thickness and drug content, results reported in the table 3.

The Thickness of the formulations was in the range of 14.23± 0.12 to 14.50± 0.06 cm which indicates uniformity for all formulations..

Weight variation was found to be in the range of 2.34± 0.12 to 4.51± 0.08%.

Hardness of the formulations was in the range of 15.95± 0.13 to 16.47± 0.08 kg/cm^2. Friability was in between 0.93± 0.13 and 0.96± 0.07%. The results of hardness and friability indicated that the Carbamazepine lozeges formulations were mechanically stable.

Drug content was found to be in the range of 95.28± 0.12 to 99.82± 0.52%.

Disintegration time of all Carbamazepine lozengesformulations lies in between 20±0.3 to 25±0.2min. Thus, it can be concluded that all the formulations passed physicochemical evaluation. In-vitro release study was performed for 30 minutes, results are shown in figure 1.The percent drug release was found in the range of 55.49 to 93.27%. Carbamazepine lozeges formulations of batch CL4 showed a release of 93.27% in 30 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. Since methylcellulose is a hydrophilic polymer, it facilitatesquick release of drug. But as the concentration crosses the optimum quantity it retards drug release[15].

During stability study of 6 months of selected Carbamazepine lozenges formulations of batch CL4, it was observed that the concentrations of drug in all the formulations were decreased a bit, within the pharmacopoeia limits.

It was found that there was a slight change in taste and color of all the lozenges.

Hence in the stability studies carried for six months it was found that there wasn't any substantial changes in hardness, friability, weight uniformity, % drug content,disintegration time the selected formulations were stable throughout the study.

Table 3: Stability study of Carbamazepine lozenges of batch CL4

Time (Month)	Hardness	Friability	Weight Uniformity	%Drug content	Disintegration time (min)
0	16.47± 0.08	0.95± 0.18	2.34± 0.12	99.82± 0.52	20±0.3
2	16.42± 0.06	0.94± 0.07	2.31± 0.23	99.81± 0.03	19.2± 0.05
4	16.39± 0.11	0.94± 0.06	2.30± 0.05	99.80± 0.02	19± 0.04
6	16.31± 0.23	0.93± 0.15	2.29± 0.09	99.79± 0.01	18.95± 0.03

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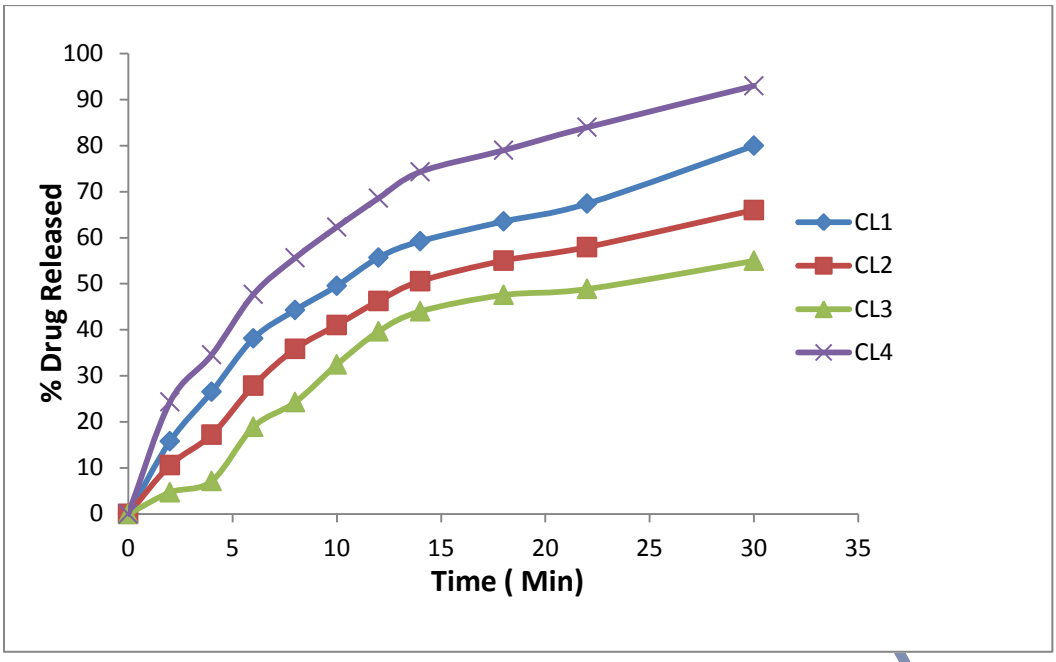

***In-vitro* drug release profile of Carbamazepine lozenges formulations**

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Conclusion

Lozenges enjoy an important position in pharmacy and will continue to remain at the same in future. From present study it is concluded thatincorporating polymers like HPMC K4M and methylcellulose can be used to formulate effective medicated Carbamazepine lozenges especially for patients who cannot swallow solid oral dosage forms like tablet and capsules. This will offer better patient compliance and innovative dosage form. Lozenges are intented to slowly dissolve in the mouth over a relatively long period of time usually about 2-15 mins or more as needed. By incorporation of synthetic polymers yields good results and release thedrugs for a prolonged period of 30 mins. Based on different parameters Carbamazepine lozenges formulations of batch CL4 can be considered as the optimized formulation.

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