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Acetazolamide Lozenges as the Promising Candidate for Prophylaxis of High Altitude Sickness

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ABSTRACT

The present study aimed to formulate and evaluate Acetazolamide as a lozenge to combat flaws in regard to conventional dosage form. Mountain sickness is a distressing disease common in the estimated hundred million who briskly ascend from lower altitudes to elevations above 2500 m. around the world. It is manifests with headache, which is often associated with fatigue, lightheadedness, anorexia, nausea, vomiting and disturbed sleep with frequent awakening. Acetazolamide is a carbonic anhydrase inhibitor works by shortening the period of high-altitude acclimatization; by inhibiting conversion of carbon dioxide to bicarbonate, the resultant metabolic acidosis may also increase oxygenation during hypoxia. Lozenges were manufactured by heating and congealing method with sucrose with dextrose as a base of lozenge and HPMC (E5) in varying concentrations. Preformulation illustrated compatibility of excipients and drugs coordinated using FT-IR. Post formulation parameters were studied. Formulation F2 was considered as excellent medicated confection that met all the requirements showing adequate hardness and disintegration of 10.3 kg/cm2 and 9.24 minutes respectively with a strong drug release rate of 99.14%. The acetazolamide lozenges can be a better approach for high altitude problems in prevention as well as treatment in emergency conditions with shorter half-life.

KEYWORDS: *Acetazolamide; Acute mountain sickness; bioavailability; high altitude; Hypoxia; Lozenges; systemic absorption.*

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INTRODUCTION

Over the past years, there has been an enhanced demand for more patient friendly and compliant dosage forms. As a result, the demand for developing novel technologies has been enhancing. Since the development of new drug molecule expensive, efforts are now being made to focus on the development of new drug dosage forms for existing drugs with improved efficacy and safety, bioavailability together with decreased dosing frequency, and the preparation of more cost-effective dosage forms. To fulfill these medical needs, pharmaceutical technologies have developed a novel oral dosage form known as lozenges tablet, Drug dissolution, absorption and onset of therapeutic effect and drug bioavailability may be significantly higher than those observed from conventional dosage forms. Lozenges offer advantage for patients who have difficulty in swallowing [1].

Lozenges are one of the most common types of solid drug forms used in the oral cavity to achieve either a systemic effect or a local action. Lozenges are solid, single-dose formulations that are sucked and dissolve or slowly disintegrate in the oral cavity, according to the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph.Eur.). Sugars such as sucrose and dextrose can be used in lozenges, as well as sugar-free formulations based on sorbitol or mannitol. Demulcents, as well as other groups and combinations, are possible. (Gelatin and/or fused sucrose) prepared by moulding and also referred as troches [20].

Advantages of Lozenges [2-4]:

A. Administration to pediatric and geriatric patients is easy.

B. Oral cavity has a local and systemic impact.
C. The drug's contact period is extended, and Long-term drug intervention
D. Drugs should not be metabolized in the first pass.
E. Intake does not necessitate the use of water.
F. Suitable for patients who have trouble swallowing (Dysphagia)
G. If the dosage is no longer needed, the lozenge may be removed.
H. Modification of the formula to meet the needs of the patient.
I. Production time is reduced, and production costs are reduced.
J. It gives the mouth flavour and a good taste.
K. Patient compliance is improved.

High-Altitude Diseases

Persons at high altitude are exposed to extremes of climatic conditions, marked by gradual reduction of barometric pressure and percentage of oxygen with rise in altitude. About 1240 million people are live in the mountains, distributed over the world. Out of these, more than 140 million are distributed at an altitude of over 2500 m. [13]. Each year, thousands of individuals move to high altitude locations worldwide for different purposes like work-related activities, or pilgrimage. Anybody moving to a high altitude is at risk of having acute mountain sickness (AMS). However, it is seen more often above 2,500 meters (8,250 feet) [5].

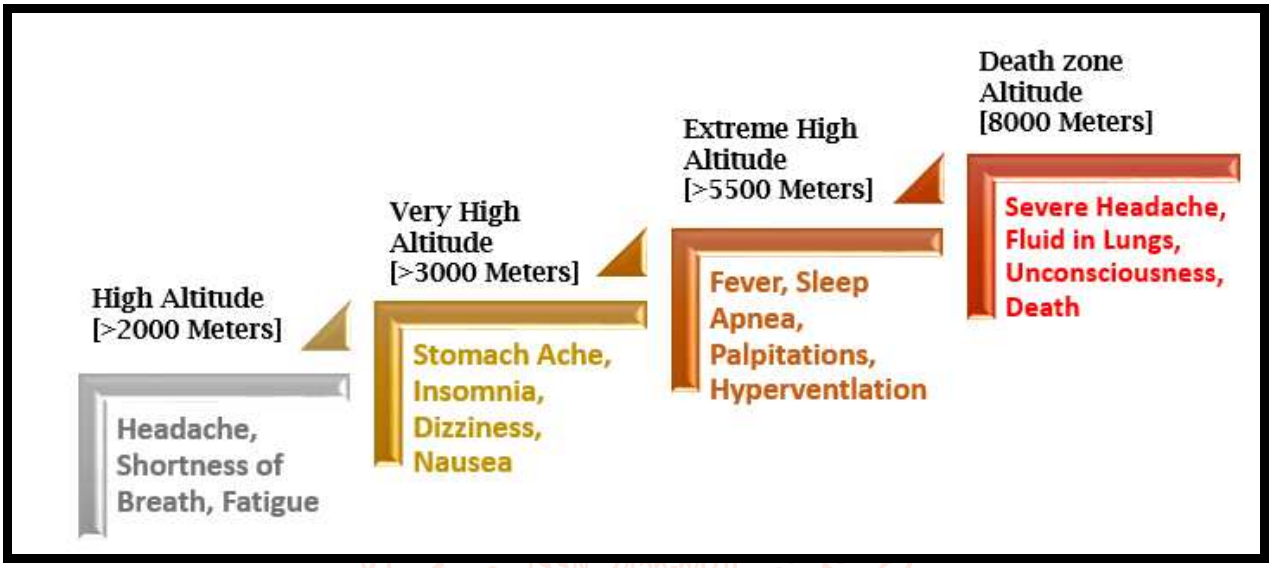

Figure No.1 High-Altitude Diseases, their Altitude of Occurrence and Symptoms

Diagnosis of Mountain Sickness [6]

If headache is only symptom, individual should stop climbing and take a mild pain reliever. If having a headache that does not go away or have other symptoms that suggest acute mountain sickness.

This illness can be diagnosed without tests.

Prevention for Mountain Sickness [7]

Progressive increase in altitude will aid body adapt to the less oxygen environment and can lowers chances of developing every forms of altitude problems. folks adapt at various rates and there are 4 general guidelines for hikers above 10,000 feet that are pragmatic for climbers to follow

A. Do not increase altitude by more than 1,000 feet per night.
B. every time one can increase his/her altitude by 3000 feet only and should spend a second night at this altitude before going farther.
C. Limit the physical exertion to reasonable levels during first few days of ascent to altitude.
D. Drink plenty of fluid during altitude exposure.

If someone develop early signs of altitude sickness, one can keep from getting worse if immediately stop ascending or descend.

If person experienced high-altitude illness in the past and are arranging to afresh go to high elevation, may wanted to moot with respective doctor the option of taking a prescription drug. The ones used are acetazolamide and the corticosteroid medicine dexamethasone.

Altitude Sickness and High Flying

Aircrafts fly at very high altitudes of nearly 30,000 to 45,000 ft. In an airplane, the cabin air pressure is set to compensate for this much altitudes. The oxygen level is equivalent to levels found in heights of 5000 to 9000

feet. Someone can be more likely to get high altitude sickness on flights if dehydrated. Over a long flight, this high altitude and factors like sitting in a chair for long hours, airline food, the time zone difference, dry air combine to make an individual feel jet lagged at the end of journey. Drinking caffeine containing drinks or alcohol before and during flight can enhance chances of experiencing symptoms. Symptoms like mild altitude sickness with headaches, muscle aches, fatigue and nausea. Age, sex, and other general physiological characteristics do not seem to make any difference in risk for altitude problems. However, while normal health may not be a risk factor for high altitude sickness, high elevations could worsen heart or lung conditions [8].

- **Practicable Risk Factors for developing High Altitude Illness from Air Travel includes :**

- Heart disease
- Lung disease
- Living at a low elevation
- Participating in a strenuous activity
- Having/had Altitude Sickness before.

- **World's Highest Civilian Airports [8]**

There are number of civilian airports which are situated at the height of above 2500 meters and may need the medical attention too. There are total 49 active airports at present which are having greater altitude and the visitors or travelers may face the problems associated with high flying. Out of all airports more than 70% of airports are located in China.

The army persons who are having their military base camps at high altitude (>2500m) are struggling to protect their camps from enemy attacks and also from natural disasters like land slide, mudslide, rockslide, avalanche (snow slide) and serac collapse. In such emergency cases or as a part of rescue team in disaster first responders and conditions like war, they need to climb up at rapid pace than normal ascent speed. Here's the chances of development of an altitude sickness in the soldiers and these sickness may be fatal and reduces the speed of whole squad. As those are emergency conditions soldier cannot take the medication prior a day as the existing dosage form suggested to do, so here's the need of the alternative dosage form which is easy to carry and possible with self-medication with a high and accurate dose, which does not required the water to uptake of medicine and last but not the least medication have pleasant taste, higher bioavailability and short half-life with other pharmaceutical advancements.

Acetazolamide as revolutionary drug for prophylaxis of altitude associate problems [09-14]

- **Synonym:** Acetazolamidum
- **Molecular Formula:** $C_4H_6N_4O_3S_2$
- **Relative Molecular Mass:** 222.2
- **Description:** A white, or almost white, crystalline powder; odourless.
- **Solubility:** Slightly soluble in ethanol, very slightly soluble in water and practically insoluble in ether R.
- **Pharmacologic Classification**: Carbonic anhydrase inhibitor.
- **Therapeutic Classification**: Altitude sickness agent (prevention and treatment). Anti-glaucoma agent, anticonvulsant, diuretic, Pregnancy risk category.
- **Storage:** It should be kept in air tight well-closed container.

- **FDA-Approved Indications of Acetazolamide [15]**:

A. Glaucoma
B. Idiopathic
C. Intracranial hypertension
D. Congestive heart failure
E. Altitude sickness
F. Periodic paralysis
G. Epilepsy

- **Mechanism of Action [16]**

Acetazolamide is a carbonic anhydrase inhibitor. It means the drug works to cause buildup of carbonic acid by avoiding its breakdown. The outcome is acidic blood (lowering blood pH), given enhanced carbonic acid, which has a reversible reaction gives bicarbonate ion with a hydrogen ion.

Carbonic anhydrase is present in red blood cells and the proximal tubule of nephrons. It work by reabsorbing chloride, bicarbonate, and sodium. As the acetazolamide inhibits carbonic anhydrase, bicarbonate, chloride and

sodium, gets excreted instead of reabsorbed; it also leads to the elimination of excess water from body. The clinical result is a lowering of blood pressure, intracranial pressure, and intraocular pressure. Bicarbonate excretion decreases the pH of the blood. Extent of aqueous humor level drops down in the eyes, as there are rectifying mechanisms to enhance blood acidity known as hyperventilation.

The complete process of inhibition that is averted by carbonic anhydrase is primarily working to increase acidity to the urine and also reuptake of bicarbonate. Drug will reverse the entire action by increasing sodium in the urine with enhancing bicarbonate which results in alkalinizing urine. Diuresis is the other result.

Materials and Methods

Acetazolamide purchased from Yarrow Chem Products, Ghatkopar (West) Mumbai and other ingredients are received through KCT'S Ravindra Gambhirrao Sapkal College of Pharmacy, Anjaneri, Nasik.

Formulation and Preparation of Hard-Candy Lozenges:

Candy base: Sucrose and dextrose are used in 65-25% ratio, which produces lozenges with adequate sweetness, resistance to moisture, graining and reactivity with medicinal components.

Colours: FDA approved food colour tartrazine (FD & C #5) are used in aqueous solution to prevent non uniformity. Artificial sweeteners and Flavours: Saccharin sodium, lemon is used for effective taste masking.

METHOD OF PREPARATION

Required quantity of sugar syrup was prepare by mixing sucrose and water. Dextrose was dissolve in small proportion of water then heated it to 110°C untill dextrose liquefy completely with forming a clear viscous syrup. Then the dextrose solution was mix into the sugar syrup and raised temperature to 160°C till the original colour changes to slight golden yellow. The temperature was bring down to 90° C and drug, polymer and other ingredients were added. The solution was poured into the mold. The final lozenges were wrap within aluminium foil and stored in desiccators to inhibit moisture absorption. The final weight of each lozenge is ≈ 3.5 gm.

Table No. 1: Details of Formulations

Sr. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6
1.	Acetazolamide	500	500	500	500	500	500
2.	Sucrose	2020	2000	1980	1960	1940	1920
3.	Dextrose	750	750	750	750	750	750
4.	Mannitol	100	100	100	100	100	100
5.	Hydroxy Propyl Methyl Cellulose	0	20	40	60	80	100
6.	Eudragit	20	20	20	20	20	20
7.	Citric Acid	30	30	30	30	30	30
8.	Sodium Saccharin	5	5	5	5	5	5
9.	Tartrazine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
10.	Lemon Oil	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Total	3425	3425	3425	3425	3425	3425

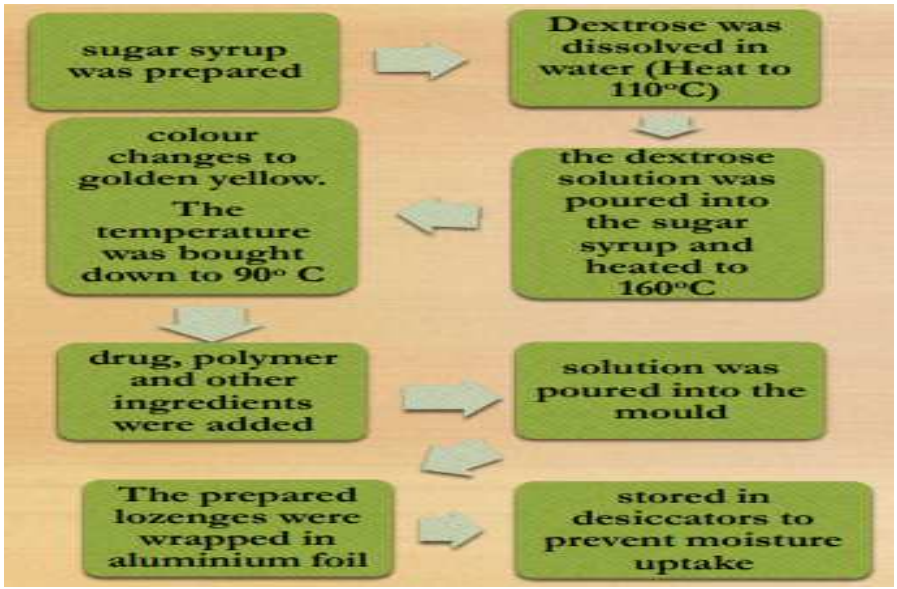

Figure no. 2: Flow Chart of Preparation Process of Lozenges

➢ **Evaluation of Acetazolamide lozenge** [17]

- **General appearance:**

The presence or absence of odour, texture of the surface and colour was determined by organoleptic evaluation.

- **Thickness:**

Thickness of the formulated lozenges were estimated in triplicates. vernier caliper is used for measurement in mm, the average of which was evaluated and regulated within ± 5% variability.

- **Hardness test:**

The final lozenges were tested for hardness by using a Monsanto hardness tester which is to be expressed in kg/cm2 and measured further was mean and standard deviations.

- **Friability test:**

The friability test was carried out by considering twenty lozenges which had been put in the roche friabilator and permitted 100 revolutions to be made. The lozenges were reweighed and dedusted. The loss weight in percentage was calculated using formulae,

Percentage friability = $\frac{w1-w2}{w1} \times 100$

Where,
W1= Initial weight of 20 lozenges.
W2= Final weight of 20 lozenges.

- **Weight Variation test:** [21]

Twenty lozenges selected randomly from lots were considered as the average weight of which was determined and compared with the individual weight.

- **Cooling Tests:**

Visual inspections of final product were conducted to check if cracks, air bubbles or black specs were present or not.

Upon which they were accepted and rejected.

- **Drug Content:**

The lozenges were powdered equivalent to 25mg which dissolved in pH 6.8 Phosphate buffer 100ml volumetric flask from which 1ml was diluted in 50ml volumetric flask and filtered by using filter paper. The absorbance was measured at 263 nm using corresponding blank. The evaluation was performed in triplicates and the calibration curve used to calculate the drug content.

- **Moisture content analysis:**

The final samples were weighed and crushed to powder into mortar and pestle and were placed into desiccator for 24 hours. After 24 hours the sample of lozenges were weighed and was determined by using the formulae.

% Moisture Content = $\frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$

- ***In-vitro* mouth dissolving time study (Disintegration Test):**

The mouth dissolving time of each lozenge was calculated by the use of USP Disintegration apparatus, in which lozenges were put in each tube of the apparatus and a time taken to fully erode the sample was taken into consideration with the aid of Phosphate buffer pH 6.8 at 37°C. The evaluation was performed in triplicates which were measured as well as presented on average.

- **Dissolution Test Parameters**

Medium : 250ml of phosphate buffer pH6.8

Rotation speed : 75 rpm

Temperature : 37±0.5ºC Sampling Volume : 5ml

Sampling Time : 4, 8, 12, 16, 20, 24 minutes

At predetermined time intervals samples of final product (5 ml) were collected and replenished with same sample volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 263nm [18].

Result and Discussion

The present study involves both pre-formulation and post-molded tests.

- **Description:**

A clear white to off white crystalline powder as per IP. The obtained drug was found to be white in colour, odourless.

- **Melting Point:**

The melting point of acetazolamide was found to be 258°C -260°C. The evaluation study was conducted using Thiele's tube apparatus. The results obtained were within the range of 256°C-260°C, thus indicating the purity of the drug sample.

- **Solubility Analysis:**

According to literature Acetazolamide is Very slightly soluble in water; slightly soluble in ethanol (~750 g/l) TS; practically insoluble in ether R.

- **Standard graph for Acetazolamide at λmax 263 nm**

About 100 mg of drug was taken and placed in 100 ml of volumetric flask, 6.8 pH phosphate buffer was used to made the volume to 100 ml, which is equal to 1000 µg/ml, using this stock solution prepare different dilutions from 4 to 28 µg/ml and the absorbance was recorded at 263 nm using UV spectrophotometer.

- **Calibration Curve of Acetazolamide in Buffer Solution (pH 6.8)**

Calibration curve of Acetazolamide was constructed in Buffer solution (pH 6.8). A linear relationship was obtained in between concentration (4-24 µg/ml) and absorbance of Acetazolamide in Buffer solution (pH 6.8) with R^2 value 0.9991 at 263 nm is shown in figure no. 3.

Table No. 2: Absorbance for Calibration Curve of Acetazolamide in Buffer Solution (pH 6.8)

Sr. no	Concentration (µg/ml)	Absorbance
1	4	0.221
2	8	0.380
3	12	0.536
4	16	0.693
5	20	0.881
6	24	1.024

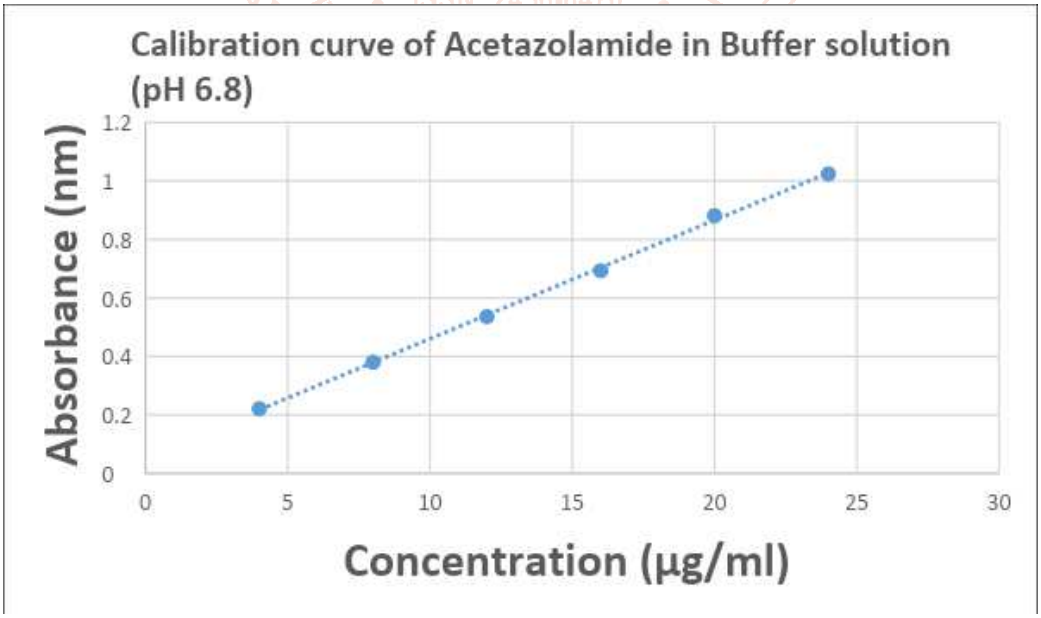

Figure No. 3: Calibration Curve of Acetazolamide in Buffer Solution (pH 6.8)

Table 3: Evaluation of Acetazolamide lozenges using different formulations

Formulation Code	Hardness (kg/cm2) Mean ± S.D	Thickness (mm) Mean ± S.D	Friability (%) Mean ± S.D	Weight variation (%) Mean ± S.D	*In-Vitro* Mouth Dissolving Time (min)	Drug content (%)	Moisture Content (%) Mean ± S.D
F1	9.7±0.53	11.00±0.0235	0.66±0.02	3436±0.1768	10.6±0.0707	97.6±0.76	0.207±0.0016
F2	10.3±0.46	12.05±0.0047	0.50±0.03	3437±0.0965	9.24±0.4714	99.8±0.51	0.191±0.0012
F3	10.5±0.52	13.10±0.0081	0.55±0.04	3515±0.1126	10.78±0.4674	98.7±0.88	0.197±0.0026
F4	10.1±0.51	11.55±0.0408	0.60±0.01	3432±0.1540	11.25±0.2041	98.2±0.71	0.200±0.0008
F5	10.3±0.83	12.50±0.0047	0.67±0.07	3575±0.1654	11.08±0.3065	96.5±0.52	0.204±0.0012
F6	11.3±0.50	13.35±0.0047	0.73±0.03	3439±0.1954	11.83±0.4478	95.3±0.19	0.188±0.0012

In all formulations, tablets weight and thickness were in mean ± 7.5% and mean ± 5% respectively. The weight variation in all the formulations was found to be, 3415-3445 mg which was in pharmaceutical limits. The thickness varies between 13.35-11 mm. Hardness of all the tablets was maintained 9.7-11.3 kg/cm^2. Assay was performed and percent drug content of all the lozenges were found to be between 95.3-99.8 %.of Acetazolamide, which was within the acceptable limits.

- **Thickness:**

Thicknesses of the formulation were found to be in the range of 11.00±0.0235 mm and 13.35±0.0047 mm. which are reported in Table 3.

- **Hardness:**

It was found to be in the span of 9.7± 0.53 and 11.3± 0.5 Kg/cm^2 as tabulated in Table 3 which were carried out in triplicates. The results derived that the lozenges have good hardness.

- **Friability test:**

Friability for all the formulations (F1-F9) was found to be within the range of 0.50± 0.03 and 0.73±0.03 as shown in Table 3.The results obtained indicated that the lozenges developed conformed to the I.P specifications (<1%) and had good mechanical strength.

- **Weight variation test:**

The average percentage deviation of all lozenges formulations was to be within the mark, and thus all formulations met the weight uniformity test according to official specifications, ranging from 3432± 0.1540 mg to 3575± 0.1654 mg. As shown in Table 3.

- **Cooling test:**

Visual inspection was conducted during the formulation process to examine any stress crack due to rapid cooling, the creation of air bubbles, surface cracking and black specs. The formulations produced were free of cracking, bubble forming and black specs when examined.

- ***In vitro* disintegration test:**

The rate of erosion of prepared lozenges ranged from 9.24± 0.4714 seconds and 18.83± 0.4478 seconds. As tabulated in Table 3.

- **Moisture analysis:**

The moisture content ranged between 0.188±0.0012 and 0.207± 0.0016, which concluded that the values were within the pharmacopoeia limits. As shown in Table 3.

- **Drug content:**

The mean drug content was registered in triplicates and was found to be between 95.3± 0.19 % and 99.8± 0.51 %. As represented in Table 3.

- **FTIR Studies:**

The FTIR spectrum of acetazolamide was recorded at wave number 4000 to 400 cm^{-1} using fourier transform spectrophotometer (Mode - FTIR, Bruker). Method used for analysis was ATR. However, ATR method is able to measure powder sample directly. Method of attenuated total reflection entails pressing the sample opposed to a high refractive index prism and estimating the IR spectrum using infrared light that is completely internally reflected in the prism. [19]

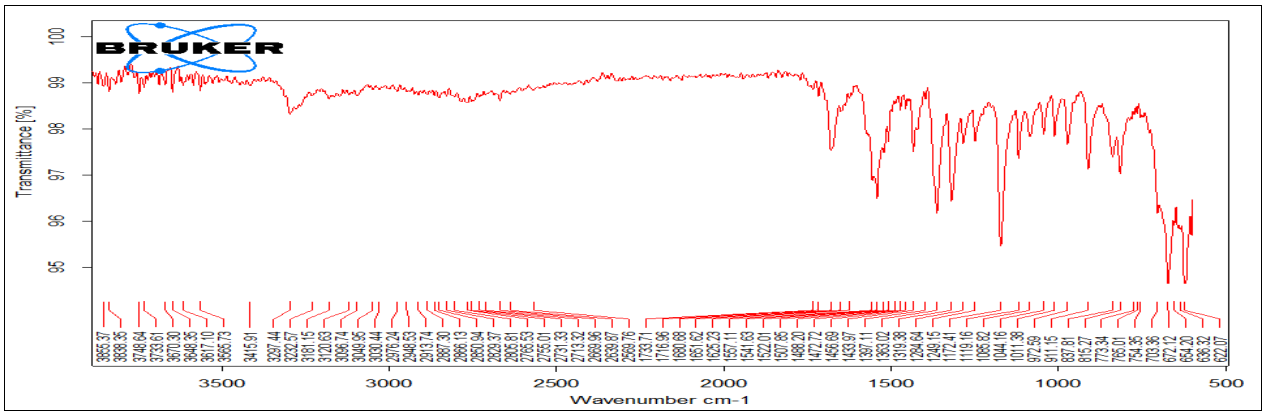

Figure No. 4: FTIR spectrum of Acetazolamide

Table No. 4: Major Peaks Observed In FTIR Spectrum Acetazolamide

Peak observed (cm^{-1})	Interpretation	Standard Value	Peak observed (cm^{-1})	Interpretation	Standard Value
3120.63	C-H stretching (aromatic)	3150-3000	1172.41	S=O stretching	1180-1050
2913.74	C-H stretching (aliphatic)	3000-2800	1733.71	C=O stretching	1870-1540
3415.91	N-H stretching	3440-3350	703.36	C-S-C	705-570
1625.23	N-H bending	1650-1580	1363.02	C-N stretching	1400-1000
672.12	C-S stretching	690-640	1557.11	C-H bending	1600-1300
1319.38	C-N-C	1320-1300	972.59	N-N stretching	980-950

The absorption bands shown by Acetazolamide are characteristics of the groups present in its molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Acetazolamide confirms the identification and purity of Acetazolamide sample.

➢ **Drug-Excipients Compatibility Study:**

Drug excipient compatibility study showed no interaction between Acetazolamide and selected excipients as there were no significant shift of peaks in the IR spectrum. So, it was concluded that the selected excipients were compatible with the drug Acetazolamide. FTIR spectrum of Physical Mixture is shown in the Figure No.5 and principle peaks are given in Table no.5.

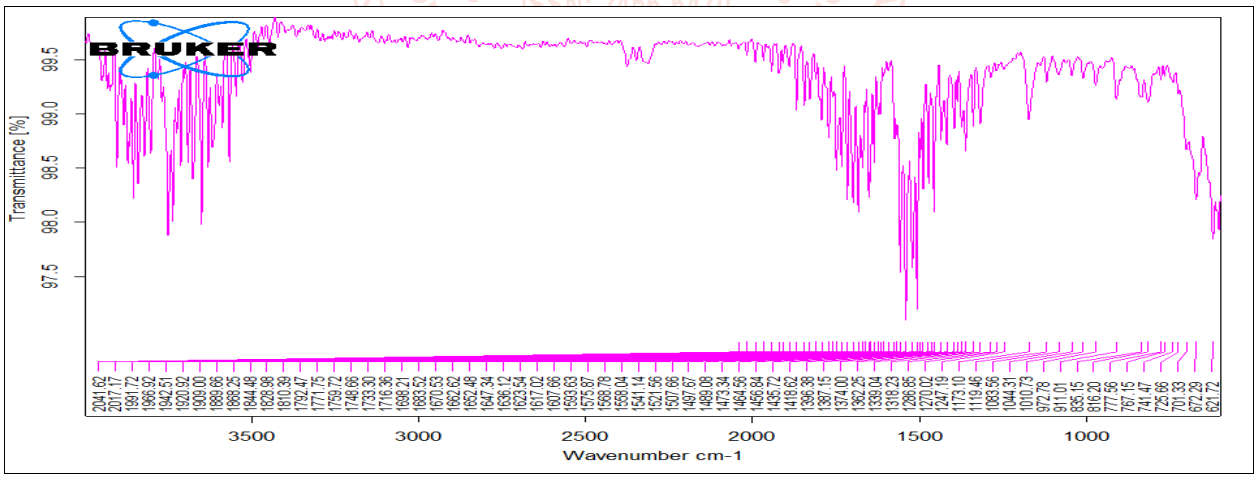

Figure No. 5: FTIR Spectrum of Physical Mixture

Table No. 5: Interpretation of FTIR Spectrum of Physical Mixture

Peak observed (cm^{-1})	Interpretation	Standard Value	Peak observed (cm^{-1})	Interpretation	Standard Value
3108.93	C-H stretching (aromatic)	3150-3000	1173.10	S=O stretching	1180-1050
2911.87	C-H stretching (aliphatic)	3000-2800	1733.30	C=O stretching	1870-1540
3417.80	N-H stretching	3350-3310	701.33	C-S-C	705-570
1623.54	N-H bending	1650-1580	1362.25	C-N stretching	1400-1000
672.29	C-S stretching	690-640	1558.04	C-H bending	1600-1300
1318.23	C-N-C	1320-1300	972.78	N-N stretching	980-950

- **Cooling Tests of Prepared Lozenges:**

Visual inspections of lozenges were conducted to check if cracks, black specs or air bubbles were present or not.

No cracks, air bubbles or black specs were present on formulation.

- ***In-vitro* Drug Release Study of Prepared Lozenges**

The percent *In-vitro* drug release of formulations has shown in following table no. 6.

Table No. 6: *In-vitro* Drug Release of Different Batches of the Formulation

Time (min.)	F1	F2	F3	F4	F5	F6
0	1.31±0.3	0.65±0.76	1.68±0.08	0.53±0.24	0.40±0.73	0.00
4	11.80±0.17	9.30±0.82	12.45±0.05	5.20±0.93	9.30±0.82	10.98±23
8	28.89±0.27	36.39±0.93	28.19±0.48	32.29±0.21	14.67±0.78	19.87±87
12	60.57±0.12	66.97±0.02	66.97±0.02	46.47±0.38	38.28±0.93	29.01±83
16	76.19±0.74	78.32±0.67	78.32±0.67	57.83±0.06	57.83±0.06	41.15±14
20	85.62±0.37	84.96±0.49	84.96±0.49	84.96±0.49	72.66±0.72	52.17±08
24	90.94±0.42	93.40±0.65	93.40±0.65	93.40±0.65	81.11±0.47	61.64±77
28	95.94±0.12	99.14±0.07	97.30±0.79	95.04±0.34	90.94±0.62	81.52±0.65

The *In-vitro* drug release study of different formulation maximum drug release 99.14% was shown by F2 batch. The data also suggested that lozenges formulation were capable to produce linear drug release. Drug release profile of formulation F1 to F3 shown in (Fig. No.6) and drug release profile of formulation F4 to F6 shown in (Fig. No.7)

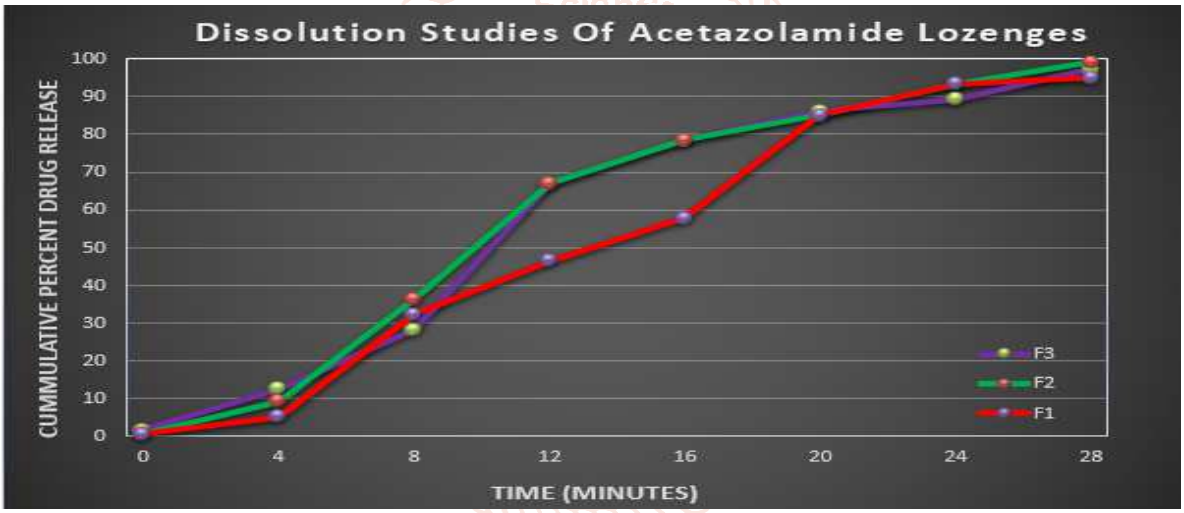

Figure No. 6: Dissolution Studies of Acetazolamide Lozenges Formulation of Batch F1, F2 and F3

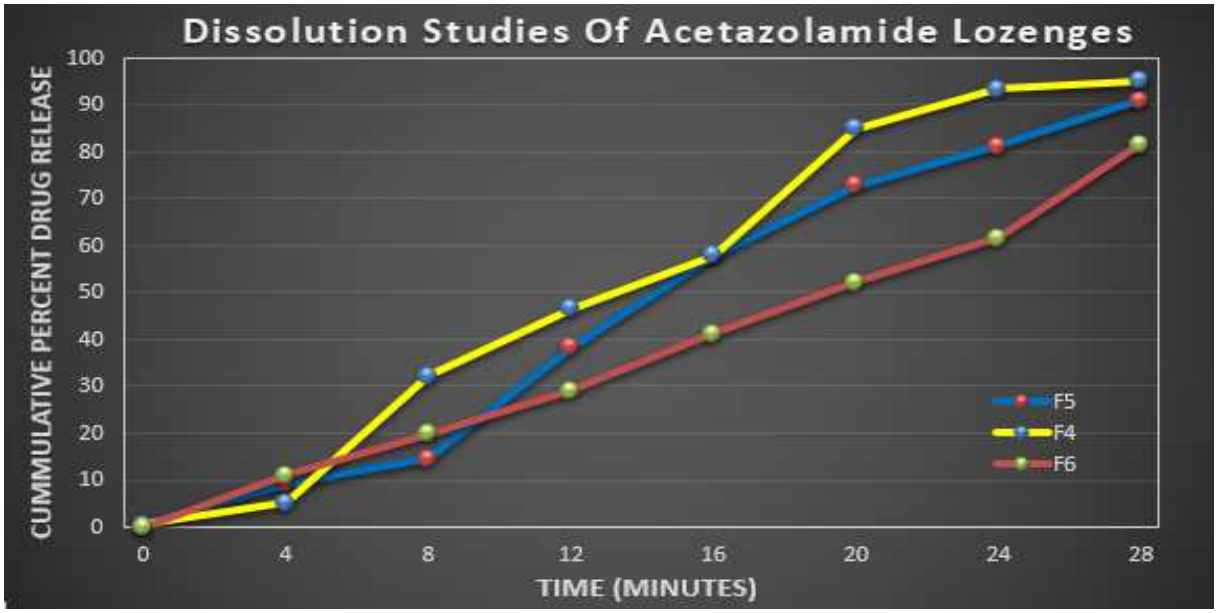

Figure No. 7: Dissolution Studies of Acetazolamide Lozenges Formulation of Batch F4, F5 and F6

- **Stability Studies of Prepared Lozenges**

All the prepared formulations were subjected to stability studies at room temperature (25±2°C and 60±5%RH) and at accelerated temperature (40±2°C and 75±5%RH) for 30 days were performed for optimized formulation (F3). Lozenges were examined at the end of 90 day for strength, drug content, and drug release percentage. Stability testes of F2 formulation showed no significant change in hardness, drug content, % drug release and other parameters. From the results obtained it was inferred that F2 was stable and retained its original properties but was found to be more stable at room temperature.

Table No. 7: Stability Test for Formulated Lozenges

Evaluation Parameters	0 Day	After Stability Study of 3 Month
Organoleptic Examination	No Change	No Change
Cooling Test	No Change	No Change
Hardness	10.3±0.46 Kg/Cm^2	9.2±0.64 Kg/Cm^2
Weight Variation	3437±0.09 %	3437±0.16 %
% Friability	0.50±0.03%	0.50±0.47%
In Vitro Mouth Dissolving Time	9.24±0.47 Min	9.00±0.88 Min
Drug Content	99.8±0.51%	98.9±0.97%
Moisture Content	0.191±0.001%	0.223±0.64%

- **Discussion**

As bioavailability is a major factor responsible for the pharmacological activity of any drug, the present work is focused on the formulation of the active pharmaceutical ingredient (APIs) as lozenges due to its various advantages. Lozenges increase bioavailability by increasing the solubility of formulation. Firstly FT-IR studies were performed and formed the FT-IR spectra, it was evident that there were no interactions between the drug and the excipients being used. The lozenges of Acetazolamide were prepared by using different concentrations of polymers by heat congealing technique (F1-F6), among the six formulations F2 (HPMC E5) showed the highest percentage of drug release, drug content, less *in-vitro* mouth dissolving time. Hence, it was observed as the improved formulation batch among the all formulations. The stability studies were performed there is no significant change in drug content, *in-vitro* mouth dissolving time, friability and weight variation.

CONCLUSION:

Acetazolamide is carbonic anhydrase inhibitor approved for the treatment of high altitude sickness orally as a tablet, capsule in the treatment or prophylaxis of high altitude sickness. Acetazolamide is a BCS class IV drug that indicates the drug has low solubility and low tissue permeability, having bioavailability of >90%. In emergency, it requires immediate release of drug from the dosage form, which make Acetazolamide suitable candidate for lozenge tablets. Lozenges are ideal for many groups of patients including pediatric, geriatrics and patients with swallowing complications, as well as for those patients having Dysphagia. By using various methods many drugs can be formulated in the form of lozenge.

The identity of Acetazolamide was confirmed by physical characteristics, spectrophotometric analysis such as Ultra violet visible spectrophotometric, Fourier Transform – Infra red studies. Lozenge tablet was made by heat molding method. Preformulation studies carried out during the early stages of the work. The drug excipient compatibility studies were carried out using Fourier Transform – Infrared to determine the interaction between drug and excipients. FTIR spectra shows there is no interaction between drug and excipients. Lozenges of Acetazolamide was then formulated followed by evaluations. In this sucrose serves as a bulking agent and sweetener in preparations. Tablets that contain high amounts of sucrose may get harden to give poor disintegration. Which is good for the hard candy lozenges. Here Eudragit providing good drug release barrier with good adhesive strength by offering best performance for enteric, protective or sustain release properties. Saccharin sodium enhances flavor systems and may be used to mask some unpleasant, unrequired taste characteristics. Mannitol it is not hygroscopic and may thus be used with moisture-sensitive preparations. Dextrose provides the rapid erosion of lozenges formulation with smooth surface texture. In oral preparation, HPMC is primarily used as a binder and as a matrix for use in extended release formulations, citric acid is used as a flavor enhancer for its tart, acidic taste. Then it will improve bioavailability by preparing lozenges of Acetazolamide using heat mold technique. Lozenge was evaluated for hardness, thickness, friability, average weight, drug content, disintegration time, drug content, in-vitro dissolution time. The thickness is observed between 11.00-13.35 mm, average weight of tablets observed between 3415-3445 mg. And

tablet hardness between 9.7-11.3kg/cm^2. Friability was measured using Roche friabilator and friability loss was between 0.50-0.73 percent. Thus, all the preparation of the lozenge tablet was complying the specifications.

The formulated tablets showed drug content between 95.3-99.8%. Disintegration time found between 9.24 - 11.83 minutes. Thus, all formulation batches of acetazolamide lozenges tablets were found to be within the acceptable range. All formulation shows good in-vitro dissolution between 81.52-99.14%.From all above study it is concluded that process parameter like hardness, thickness & friability has great influence on performance of the lozenges.

The hard candy lozenges containing acetazolamide were prepared. The effect of formulation variables on acetazolamide lozenges were studied. The concentration of HPMC had significant effect on % drug release and hardness. However the drug release was greatly retarded as the concentration of HPMC increases and drug content was decreased.

F2 formulation shows superior result than other formulation batches i.e. disintegration time (9.24 minutes), cumulative percentage drug release (99.14%) and drug content (99.80%), F2 formulation contains (HPMC 20mg and sucrose 2gm) which gives maximum drug release and minimum disintegration time and maximum drug content.

Thus it can be concluded that the acetazolamide lozenges can be a better approach for high altitude problems in prevention as well as treatment in emergency conditions with shorter half-life.

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