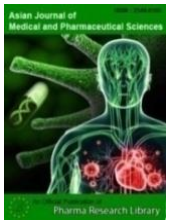

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Formulation and Evaluation of Mouth Dissolving Tablets of Hydroxyzin Hydrochloride

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A B S T R A C T

The objective of the present investigation was to formulate and evaluate of mouth dissolving tablets of Hydroxyzine hydrochloride. Mouth dissolving tablets of Hydroxyzine hydrochloride will dissolve in the patient mouth without need of water or chewing and release its drug contents instantaneously. So this dosage forms more comfortable for paediatric patients. Tablets were prepared direct compression method using Crospovidone Sodium starch Glycolate and croscarmellose sodium as super disintegrants, Orange Flavour were used as sweetening agents. The tablets were evaluated for weight variation, hardness and friability data indicated good mechanical strength of tablets. The results of in –vitro disintegration time indicated that the tablets were dispersed rapidly in the mouth with in 3.84minutes. It was concluded that mouth dissolving tablets of Hydroxyzine hydrochloride

Keywords: Hydroxyzine hydrochloride, Crospovidone Sodium starch Glycolate, croscarmellose sodium.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Fast disintegrating tablet (FDT) is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT.

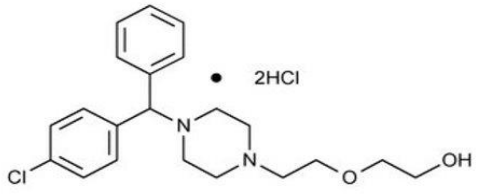

Fig.1: Hydroxyzine hydrochloride

Drug category : antihistamine
Chemical name/ Nomenclature / IUPAC Name:
2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)ethan-1-ol dihydrochloride
Molecular Formula: $C_{21}H_{29}C_{l3}N_2O_2$
Molecular Weight : 447.826 gm/mole.
Official Pharmacopoeia : USP

Physicochemical properties:

Description (Physical State): White Odorless Powder
Solubility: Soluble in water (<700mg/mL), ethanol (220 mg/mL), chloroform (60mg/mL) or acetone (2mg/mL).
Stability: stable for 366 days when stored at 4 degrees C and 25 degrees C.
Melting point: 180-220°C

pKa(strongest acidic): 15.12
Log P: 3.43
Storage Conditions: Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Pharmacokinetic properties:

Bioavailability : 80%
Half-life : 14-25hrs
Absorption : The absolute bioavailability of hydroxyzine has not been ascertained, as intravenous formulations are unavailable due to a risk of hemolysis. Hydroxyzine is rapidly absorbed from the gastrointestinal tract upon oral administration.
Volume of Distribution : 16.0 ±3.0 L
Protein binding : 93 %
Metabolism: Hydroxyzine is metabolized in the liver by CYP3A4 and CYP3A5.18 While the precise metabolic fate of hydroxyzine is unclear, its main and active metabolite (~45 to 60% of an orally administered dose), generated by oxidation of its alcohol moiety to a carboxylic acid, is the second-generation antihistamine cetirizine. Hydroxyzine is likely broken down into several other metabolites, though specific structures and pathways have not been elucidated in humans.
Metabolites : Cetirizine, others.
Time of peak action : 2hr
Excretion : 70 % via Urine, feces
Adverse effects/Side effects: Chest pain, discomfort, or tightness. difficulty with swallowing, dizziness, puffiness or swelling of the eyelids or around the eyes, face, lips, or tongue.

Pharmacodynamics:

Mechanism of action: The H1 histamine receptor is responsible for mediating hypersensitivity and allergic reactions. Exposure to an allergen results in degranulation of mast cells and basophils, which then release histamine and other inflammatory mediators. Histamine binds to, and activates, H1 receptors, which results in the further release of pro-inflammatory cytokines, such as interleukins, from basophils and mast cells. These downstream effects of histamine binding are responsible for a wide variety of allergic symptoms, such as pruritus, rhinorrhea, and watery eyes.

2. Methodology

0.2M Potassium dihydrogen orthophosphate solution:
Accurately weighed 27.218gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 mL of distilled water and mixed.

0.2M sodium hydroxide solution: Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed

pH 6.8 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 112.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Analytical method Development

a) Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in 6.8 phosphate buffer UV spectrum was taken using Lab India Double beam UV/VIS spectrophotometer (Lab India UV 3000+). The solution was scanned in the range of 200 – 400 nm.

b) Construction of standard graph

100 mg of Hydroxyzine Hydrochloride was dissolved in 100 ml of pH 6.8 phosphate buffer to give a concentration of 1mg/ml (1000 µg/ml). From the above standard solution (1000 µg/ml) 1ml was taken and diluted to 100ml with pH 6.8 phosphate buffer to give a concentration of 0.01mg/ml (10µgm/ml). From this stock solution aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml,1ml were pipette out in 10 ml volumetric flask and the volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 10, 20, 30, 40and 50µg/ mL respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) i.e., 232 nm.

Formulation Development:

- Drug and different concentrations of super Disintegrates (Cros povidone, Sodium starch Glycolate, Cros Povidone) and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes.
- The obtained blend was lubricated with Magnesium stearate and glidant (Aerosil) was added and mixing was continued for further 5 minutes.
- The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Evaluation of tablets:

Pre compression parameters:

Measurement of Micromeritic Properties of Powders

1. Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$\tan \theta = h/r$ ..... (1)

Where, h and r are the height and radius of the powder cone.

2. Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_0 is noted. The bulk density is calculated in g/cm^3 by the formula.

Bulk density = M/V_0 …….. (2)

M = Powder mass

V_0 = apparent unstirred volume

3. Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping

of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are proceeded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less the 2%, V_b is considered as a tapped volume V_f. The tapped density is calculated in g/cm^3 by the formula.

Tapped density=M/V_f ..... (3)

M =weight of sample power taken

V_f =tapped volume

4. Compressibility Index

The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) /TD] x100 …….. (4)

5. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. It is calculated by the following equation.

$H = \rho T / \rho B$ …….. (5)

Where ρT = tapped density, ρB = bulk density

Post compression parameters:

a) Thickness

The thickness of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

b) Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

c) Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

Friability = $([w_O - w] / w_O) \times 100$

Where; w_O = weight of the tablet at time zero before revolution.

w = weight of the tablet after 100 revolutions.

d) Drug content

The content of drug carried out by five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 272 nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

e) Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

f) Dissolution test of Hydroxyzine Hydrochloride tablets

- Drug release from Hydroxyzine Hydrochloride tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 medium as the dissolution medium of quantity 900 ml. The whole study is being carried out at a temperature of 37^0 C and at a speed of 75rpm.
- 5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10,15,20, 30, 45, minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV spectrophotometer. The concentration was calculated using standard calibration curve.

Drug-Excipients compatibility studies:

Drug Excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly. Fourier Transform Infrared Spectroscopy (FTIR) studies were performed on drug, optimized formulation using Bruker FTIR. The samples were analyzed between wave numbers 4000 cm^{-1} and 550 cm^{-1}.

3. Results and Discussion

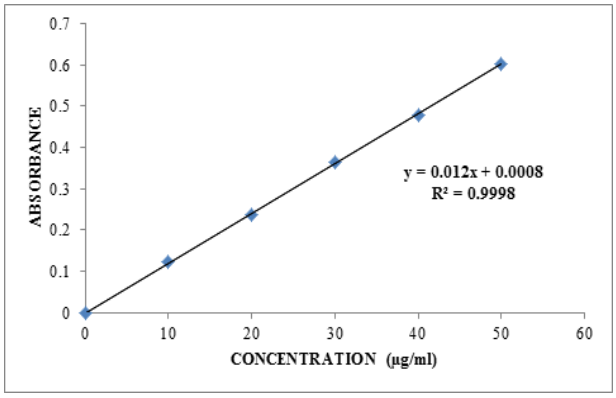

Fig.2: Calibration curve of Hydroxyzine Hydrochloride

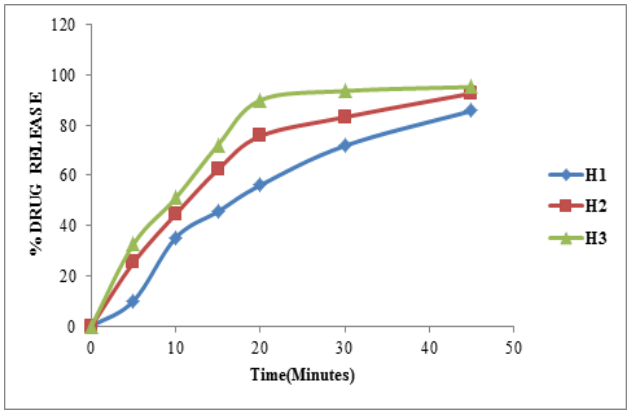

Fig.3: Dissolution profile of formulations H1, H2, and H3

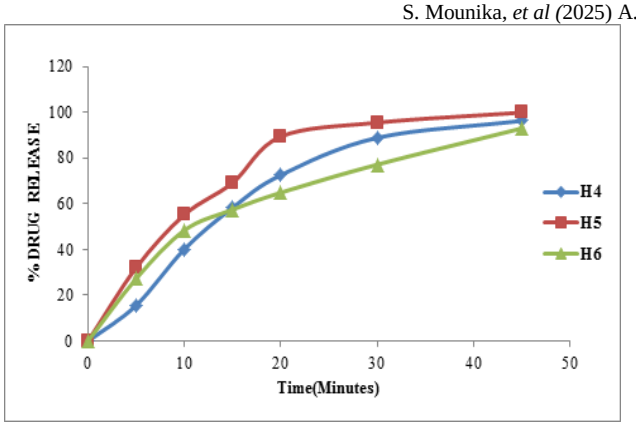

Fig.4: Dissolution profile of formulations H4, H5, and H6

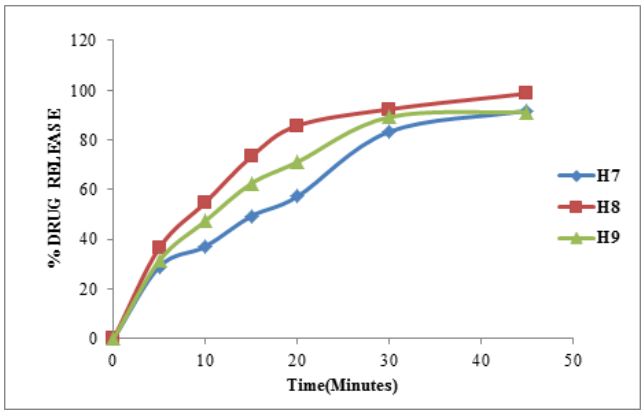

Fig.5: Dissolution profile of formulations H7, H8 and H9

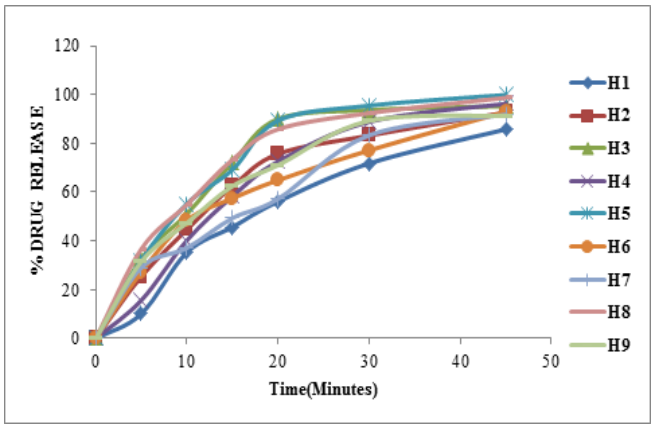

Fig.6: Dissolution profile of all formulations H1- H9

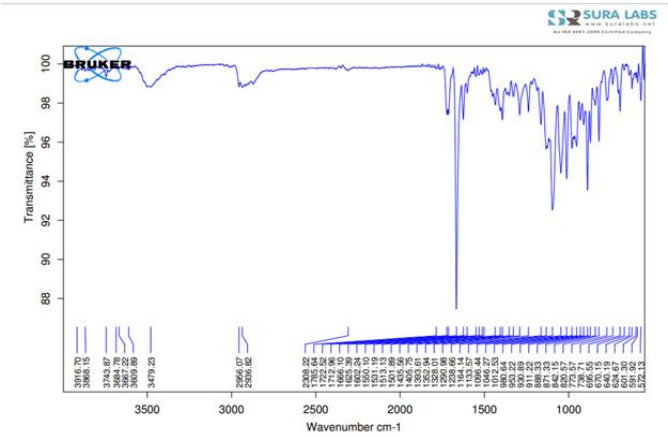

Fig.7: FTIR of Hydroxyzine Hydrochloride Pure drug

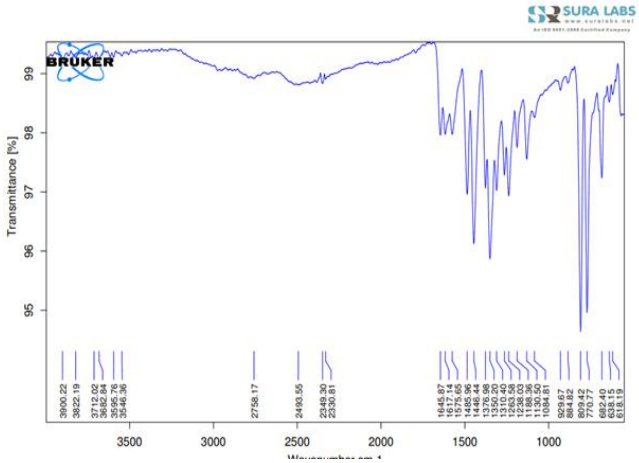

Fig.8: FTIR of Hydroxyzine Hydrochloride optimized Formulation

Table.1: Calibration curve data of Hydroxyzine Hydrochloride in ph 6.8 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
10	0.124
20	0.238
30	0.365
40	0.479
50	0.604

Discussion

From the results it was evident that the formulations prepared with Cros povidone were showed good drug release i.e., 95.25% (H3 Formulation) in higher concentration of blend i.e. 30 mg. Formulations prepared with Sodium starch Glycolate showed good drug release i.e., 99.89% (H5 Formulation) in 20 mg concentration when increase in the concentration of Sodium starch Glycolate drug release retarded. Formulations prepared with croscarmellose sodium showed maximum drug release i.e., 98.72% (H8Formulation) at 20mg of blend. Among all formulations H5 formulation considered as optimised formulation which showed maximum drug release at 45min. i.e. 99.89 %. Sodium starch Glycolate were showed good release when compared to Cros povidone, croscarmellose sodium. Finally concluded that H5 formulation (Sodium starch Glycolate) was optimized better formulation.

4. Conclusion

Mouth dissolving tablets of Hydroxyzine hydrochloride were prepared by direct compression method using Cros povidone, Sodium starch Glycolate and croscarmellose sodium as superdisintegranst. The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability. In vitro drug release from the tablets shows significantly improved drug dissolution. The In vitro drug release from formulation containing super disintegrates Sodium starch Glycolate was found to be 99.89%. Hence it could be concluded that the super diintegrant based mouth dissolving tablets of Hydroxyzine hydrochloride would be quite effective in providing quick onset of action.

Table.2: Formulation table showing various compositions

Ingredients	H1	H2	H3	H4	H5	H6	H7	H8	H9
Hydroxyzine hydrochloride	10	10	10	10	10	10	10	10	10
Cros povidone	10	20	30	-	-	-	-	-	-
Sodium starch Glycolate	-	-	-	10	20	30	-	-	-
Cros Povidone	-	-	-	-	-	-	10	20	30
Orange Flavour	2	2	2	2	2	2	2	2	2
Aerosil	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3	3	3	3
Mannitol	65	55	45	65	55	45	65	55	45
Total Weight	100	100	100	100	100	100	100	100	100

Table.3: Evaluation of pre-compression parameters of powder blend

Formulation Code	Angle of Repose (°)	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
H1	25.01	0. 59	0.57	14.03	1.16
H2	26.8	0. 46	0.67	16.41	1.19
H3	27.7	0. 32	0. 54	18.75	1.23
H4	25.33	0.54	0.64	15.62	1.18
H5	25.24	0.52	0.65	18.46	1.22
H6	28.12	0. 46	0. 56	15.15	1.17
H7	27.08	0.58	0.69	15.94	1.18
H8	25.12	0.48	0.67	15.78	1.18
H9	26.45	0.54	0.65	16.92	1.25

Table.4: Evaluation of post compression parameters of Hydroxyzine Hydrochloride Fast dissolving tablets

Formulation codes	Average Weight(mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* Disintegration Time (min)
H1	99.34	2.25	0.21	1.71	98.03	4.31
H2	98.36	2.38	0.34	1.65	97.31	4.85
H3	101.98	2.61	0.29	1.57	99.08	5.20
H4	99.12	2.36	0.36	1.69	99.22	5.33
H5	100.22	2.45	0.12	1.52	100.12	3.84
H6	98.08	2.37	0.26	1.48	97.46	4.63
H7	97.64	2.53	0.39	1.62	98.69	4.59
H8	102.79	2.44	0.44	1.59	98.28	5.21
HS9	105.62	2.58	0.28	1.66	99.35	5.93

Table.5: Dissolution data of Hydroxyzine Hydrochloride

Time (Min)	H1	H2	H3	H4	H5	H6	H7	H8	H9
0	0	0	0	0	0	0	0	0	0
5	10.11	25.42	32.73	15.62	32.06	27.26	29.05	36.69	31.48
10	35.28	44.63	51.08	40.13	55.21	48.39	37.12	54.85	47.36
15	45.69	62.39	72.19	58.27	69.17	57.44	49.37	73.34	62.48
20	56.12	75.67	89.99	72.52	89.35	64.86	57.22	85.77	71.08
30	71.83	83.22	93.64	88.83	95.48	77.14	83.32	92.38	89.22
45	85.77	92.69	95.25	96.26	99.89	92.97	91.78	98.72	91.31

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