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Research Article

FORMULATION AND EVALUATION OF SUBLINGUAL TABLET CONTAINING ANTIEMETIC DRUG

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ABSTRACT

The aim of the present research is to formulate a sublingual tablet of antiemetic drug. Doxylamine succinate is an antihistaminic commonly used for the prevention and treatment of nausea and vomiting. Oral bioavailability of doxylamine succinate is low and shows extensive hepatic metabolism. The Objective of the present research is to formulate doxylamine succinate sublingual tablet to avoid hepatic first pass metabolism and to improve its bioavailability. Sublingual route not only overcome the problem of dysphagia but also giving the rapid onset of action by enhancing permeability through site of administration

Keywords: Sublingual tablet, Doxylamine succinate, Antiemetic, Dysphagia, Bioavailability

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INTRODUCTION

In terms of permeability, the sublingual area of the oral cavity (i.e. the floor of the mouth) is quite successful than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The absorption potential of oral mucosa is influenced by the Passive diffusion involves the movement of a drug from the region of higher concentration to the region of lower concentration across biological membrane Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect.¹

The sublingual tablets are usually small, flat and compressed lightly to keep them soft. These tablets are designed in such a way that they must dissolve quickly in small quantity of saliva and allow the drug to be absorbed through the sublingual mucosa. The various types of sublingual tablets commonly used are Fast disintegrating sublingual tablets, Bio adhesive sublingual tablets and Lipid matrix sublingual tablets.²

Doxylamine succinate N-dimethyl-2-(1-phenyl-1-pyridin-2-ylethoxy)ethanamine is a first generation

antihistamine that is used for symptoms of allergic rhinitis, common cold and as a short acting sedative. The drug has activity and absorbed orally only 24.7% due to hepatic metabolism with peak plasma concentrations achieved in 6-12 hours following oral administration of therapeutic doses.

MATERIAL AND METHODS

Materials

Doxylamine succinate was a gift sample obtained from Microlabs, Mumbai. Sodium Starch Glycolate, Microcrystalline cellulose, Mannitol, Sodium saccharine, Magnesium stearate, Talc, Isopropyl alcohol were purchased from Kasliwal Brothers, Indore. Kyron-134 was obtained as gift sample from Coral-pharmachem, Ahmadabad. All chemicals were used of analytical grade.

Methods

Analytical Methods

Melting point determination

Capillary tube was taken and one end was sealed by heating. Capillary tube was filled with drug powder up to 2-3mm high. The capillary tube was putted inside melting point apparatus and temperature was increased slowly. The temperature was noted when the drug gets starts melting and again noted when drugs completely melted.

UV Spectroscopy

50mg of Doxylamine succinate was weighed and dissolved into 50ml of distilled water to prepare a 1000µg/ml stock solution from which a 10µg/ml dilution was prepared. Baseline correction was performed using distilled water and sample was run between 200-400nm wavelength range in spectrum mode.

Calibration curve

The calibration curve of Doxylamine succinate were prepared in distilled water and 6.8 pH phosphate buffer by using Shimadzu 1800 UV visible spectrophotometer.

Accurately weighed 50mg of Doxylamine succinate was transferred into a 50ml volumetric flask and the volume was made up with distilled water to obtain a 1000µg/ml stock solution of Doxylamine succinate.

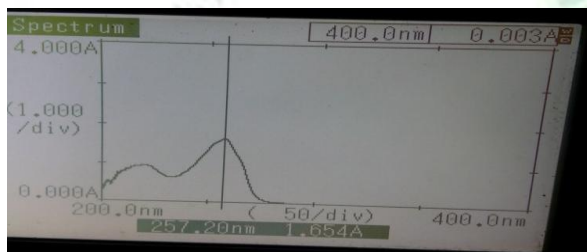


Figure 1: Lambda Max of Doxylamine succinate

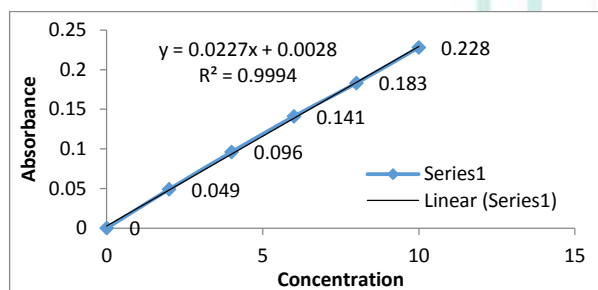


Figure 2: Calibration curve of Doxylamine succinate

From the stock solution 1ml was taken and transferred into a 10ml volumetric flask and rest of the volume was made up with methanol to obtain a 100µg/ml of solution from which 1 to 10µg/ml dilutions were prepared. Same procedure was followed for distilled water to prepare calibration curve respectively.³

Solubility studies

The solubility of Doxylamine succinate in various medium was determined by shake flask method. In this method 2ml of each solvent was taken into a vial and an excess amount of Doxylamine succinate was added. The vials were sealed properly and stirred for 10min. They were then kept on orbital flask shaker at 37°C for 24h. After solubilization of Doxylamine succinate, an extra amount of Doxylamine succinate was added to the vials containing drug-solvent mixture. The process was repeated until saturation solubility of Doxylamine succinate, indicated by presence of undissolved drug. The mixtures were then kept at room temperature for 24 h. and centrifuged using Remi12C micro-centrifuge at 3000RPM for 15min. The supernatant were separated and diluted with respective solvents. The drug concentration was analyzed spectrophotometrically at 262 nm using UV-visible spectrophotometer (Shimadzu-1800).³

Formulation

Taste Masking

Doxylamine succinate and Kyron 134 was taken in 1:5 ratios for taste masking. Kyron 134 was added to 25ml of distilled water in a beaker. The mixture was stirred for half an hour. Doxylamine succinate was added to it and the mixture was stirred for 2 hours at 1000 rpm. The complex was filtered using Whatman filter paper. The above mixture was dried.

Experimental design

A central composite design for two factor three level was selected to optimize the variable response. The two factors, viz. Polymer X₁ Kyron-134 and Polymer X₂ Sodium Starch glycolate of each polymer blend, were required by the experimental design and the factor level were suitably coded. The amount of Magnesium stearate, Talc, Sodium Saccharine and mannitol was kept constant, while Microcrystalline cellulose was taken in a sufficient quantity to maintain a constant tablet mass of 120mg. time taken to release 90% of drug were taken as the variable response.

Table 1: Composition of various formulations of tablets

S.no.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Doxylamine succinate	50	50	50	60	60	60	70	70	70
2.	Sodium starch glycolate	52.5	42.5	32.5	42.5	32.5	22.5	32.5	22.5	11.5
3.	Microcrystalline cellulose	10	20	30	10	20	30	10	20	30
4.	Mannitol	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
5.	Sodium saccharine	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
6.	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7.	Talc	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25

Precompression evaluation (Drug excipients mixture)

Bulk density

Bulk density is defined as the ratio of mass of the powder to the bulk volume of the powder. 10gm of powder were taken in a 100ml measuring cylinder and noted down the volume occupied by the powder.

Tapped density

Tapped density is defined as the ratio of the mass of the bulk powder to the tapped volume of the powder. 10gm of powder were taken in a 100ml measuring cylinder and noted down the volume occupied by the powder after tapping.

Angle of repose

Angle of repose is a characteristic related to inter-particulate friction. The angle of repose was performed to determine the flow property of the formed powder. Set the funnel 4cm above the working slab. Pour the powder through funnel until pile of powder touches the funnel. Note the height and diameter/radius of the pile of powder. Determine angle of repose by applying the formula.

$$\tan\theta = h/r$$

where θ = angle of repose

h = height of pile

r = radius of pile

Hausner's ratio

Flow ability of a powder was evaluated by comparing the bulk density and tapped density of a powder. It is an indication of compressibility of a powder. It measures the relative significance of interparticle interactions. A Hausner's ratio of <1.25 indicates a powder that is free flowing whereas >1.25 indicates poor flow ability of powder.

20gm powder was taken in measuring cylinder. Note the poured volume of powder. Now it was tapped for 100 times. Tapped volume of powder was noted. Poured density and tapped density by applying the formula was determined.

$$\text{Poured density} = \frac{\text{mass of powder}}{\text{Poured volume of powder}}$$

$$\text{Tapped density} = \frac{\text{mass of powder}}{\text{Tapped volume of powder}}$$

Determine Hausner's ratio and Carr's Index

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Preparation of Doxylamine succinate Sublingual tablet by direct compression method

- Weigh all Ingredients as per the quantities defined in table no. 1
- Pass all the ingredients through sieve #80 and collect individuals in polybags.
- Mix measured quantity of Doxylamine Succinate and kyon 134, sodium starch glycolate, MCC, Mannitol and Sodium Saccharine for 15 minutes in a polybag.

- Magnesium stearate and talc was added to it and blend for 5 min in pastle mortar.
- Compress final blend using B-Tooling, multiple rotatory compression machine using 6 mm round shaped punches and corresponding dies.

Evaluation of Tablet

Weight variation

Weighed individually 20 tablets selected at random. Calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than percentage shown in the table and none deviates by more than twice that percentage. If more than two tablets deviate from the range, retest 20 tablets are done and not more than 2 tablets should deviate from 40 tablets.

Thickness

Set scale to zero. Place the tablet laterally between the jaws of vernier caliper. Make sure jaws shall just touch object to be measured. Record the reading displayed. Take out the sample, clean the jaws and keep the caliper in place.

Hardness

Place the tablet on the holder. Set the "0" on Monsanto tester scale. Press the tablet. The range of Monsanto hardness tester is "0 to 20" kg. When tablet breaks read the pressure applied and cleans the holder.

Friability

Connect the main socket. Weigh the tablets before placing it in friability apparatus. Place 10 tablets in the friability test apparatus. Switch "ON" the mains. Take out tablets after 100 revolutions has completed. Reweigh the tablets after dedusting. Switch "OFF" the mains. Clean the friability test apparatus.

Wetting time

The tablet was placed at the center of two layers of absorbent paper fitted into a petridish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch. The evaluation parameters of batches F1 – F9 are shown in table.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was the reweighed. Water absorption ratio, R was determined using following equation

$$R = 100 \times \frac{W_a - W_b}{W_a}$$

Where, W_a = Weight of tablet after water absorption

W_b = Weight of wetted tablet before water absorption

Disintegration Time

One tablet was introduced into each tube and disc was added to each tube. The assembly was introduced in the

beaker containing purified water. The apparatus operated until the tablet completely disintegrate. The time was noted down until the tablets completely disintegrate without any remittants. The assembly was removed from water.

In vitro Dissolution

Switch ON the mains from electric board. Adjust/maintain temperature from heater knob. Maintain the water level in the water bath up to the specific mark. Place 900 ml of buffer in dissolution vessel and adjust temperature between 36.5-37.5 °C. Shaft is positioned in such a way that its axis is within 2 mm of axis of the vessel and lower edge of blade is 23-27 mm from the inside of bottom of vessel. Lower down the paddle in the vessel. Put on tablet in the vessel. Immediately ON the apparatus at 50 rpm for 30 min. Withdraw 5 ml sample at every 5 minutes interval and replace by volume of dissolution medium equal to the volume of sample removed. Filter the samples using whattman filter paper. Prepare appropriate dilutions and analyze the samples with UV spectrophotometer at λ_{max} 262 nm. Determine the concentration and percentage drug release. Switch OFF heater and main of the apparatus.

Stability studies

The stability studies were carried out for a period of 1 month in the stability chamber. The tablets were stored under the following conditions as prescribed by the ICH guidelines (40°C±2°C and 75±5% RH Q1C). The tablets were withdrawn periodically with an interval of 30 days and analyzed for Hardness, Disintegration, Dissolution, Wetting time, drug content etc.

RESULT AND DISCUSSION

Doxylamine succinate sublingual tablet was formulated. Total nine batches were prepared for sublingual formulation. All the formulations were subjected to evaluation, Tablet weight varied from 110 to 120 mg, and thickness 3 to 4.1 mm. Tapped density of formulation F2 was highest among the all formulations. All the tablets exhibited friability values between 0.5 to 0.8. Tablets from Formulation F2 have shown lowest friability among the all formulations. All tablets disintegrated in less than 1 minute. The drug released at the time interval of 30 minutes up to 97.5% of batch F9. Initial release rate was found slow in case of formulation F1 & F2 as compared to other formulations.

Table 2: Evaluation of Flow properties of powder (Drug excipient mixture)

Characterization	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density	0.100	0.100	0.95	0.100	0.095	0.100	0.105	0.100	0.100
Tapped density	0.117	0.125	0.117	0.111	0.117	0.125	0.117	0.111	0.117
Carr's index	14.25	20.00	18.80	9.90	18.80	20.00	10.25	9.90	14.52
Hausner's ratio	0.17	1.25	1.23	1.11	1.23	1.25	1.11	1.11	1.17
Angle of repose	27.92	26.56	28.36	27.92	26.10	28.81	27.02	27.02	29.68

Table 3: Determination of physicochemical properties of sublingual tablet

Batch	Hardness (Kg/cm ²) ±SD	Thickness (mm) ±SD	Percent Friability (%)±SD	Weight variation (mg) ±SD
F1	2.833±0.057	3.9±0.199	0.853±0.0057	118.33±2.081
F2	2.9±0.00	3.73±0.057	0.776±0.0152	114.33±0.577
F3	2.76±0.057	3.83±0.115	0.823±0.0115	116.33±1.527
F4	2.86±0.115	3.76±0.115	0.846±0.0057	114.66±2.081
F5	3.16±0.057	3.93±0.115	0.783±0.0115	117.66±1.154
F6	2.833±0.057	3.7±0.099	0.580±0.010	113±3.00
F7	3.03±0.057	3.96±0.152	0.686±0.0057	117.33±0.577
F8	2.86±0.057	3.93±0.057	0.826±0.0251	117.33±1.527
F9	3.16±0.057	4.03±0.057	0.686±0.0057	119.33±0.577

Table 4: Other Evaluation parameters

Batch	Drug Content Uniformity	Wetting Time(Sec.)	Water Absorption ratio	Disintegration Time(Sec.)
F1	93.33±2.516	24.33±4.041	51±2.645	106±6.92
F2	89.66±0.5773	22±3.605	49.33±0.577	56.66±3.214
F3	93.66±3.785	22.33±1.527	44.66±4.163	69.66±1.527
F4	96±3.6055	26±4.582	42±3	65±3
F5	98.33±0.5773	18.66±0.577	40±1	53.66±2.309
F6	95±2.645	22.33±2.516	42.33±2.309	53±3.605
F7	98.33±0.5773	18.66±1.527	35±3.605	54.33±4.041
F8	93.66±4.041	22±2.645	36.66±2.516	53±4.582
F9	98.66±0.577	17.66±0.577	32.66±0.577	48.33±0.577

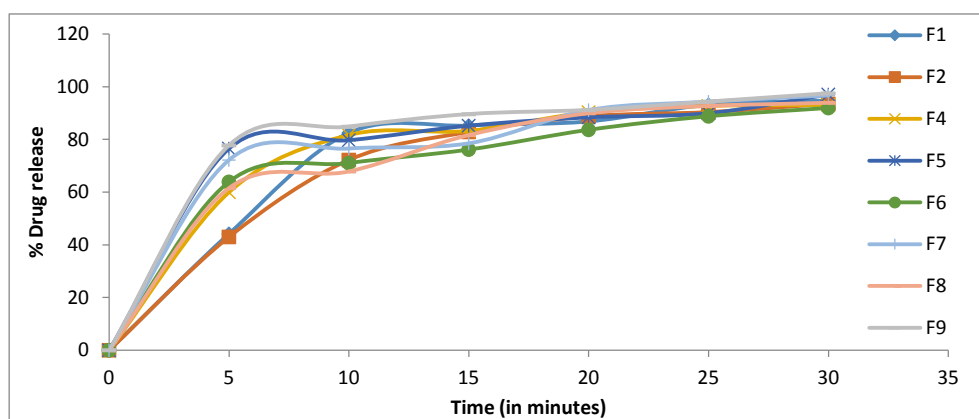


Figure 2: *In-vitro* drug release of sublingual tablet

Table 5: Stability studies

S.No.	Parameter	After 30 days	Inference
1.	Weight variation	119.33±0.574	Within Limit
2.	Hardness	3.16±0.055	Within Limit
3.	Drug content	98.66±0.578	Within Limit
4.	Wetting time	17.66±0.574	Within Limit
5.	Water absorption ratio	32.66±0.576	Within Limit
6.	Disintegration	48.33±0.575	Within Limit

CONCLUSION

The present study was carried out to prove that sublingual tablet of Doxylamine succinate can be formulated. The concept explains that formulated doxylamine succinate sublingual tablet avoids hepatic first pass metabolism and improves its bioavailability.

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