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FORMULATION AND EVALUATION OF MATRIX TABLET OF DOXOFYLLINE

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ABSTRACT

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible Asthma is the result of chronic inflammation of the airways which subsequently results in increased contractability of the surrounding smooth muscles. This among other factors leads to bouts of narrowing of the airway. The narrowing is typically reversible with or without treatment. Occasionally the airways themselves change. Common symptoms include wheezing, coughing, chest tightness.

Keywords: Asthma, chronic inflammatory disease, COPD.

1. INTRODUCTION

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction and bronchospasm.[1] Asthma is the result of chronic inflammation of the airways which subsequently results in increased contractability of the surrounding smooth muscles. This among other factors leads to bouts of narrowing of the airway. The narrowing is typically reversible with or without treatment. Occasionally the airways themselves change. Common symptoms include wheezing, coughing, chest tightness, and shortness of breath.

Drug Analysis

Melting Point

It was one of the parameters to judge the purity of crude drugs. In case of pure chemicals or photochemical, melting points are very sharp and constant. Since the crude drugs contain the mixed chemicals, they are described with certain range of melting point.

Procedure:-

A small quantity of powder was placed into a Capillary. That was placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

Drug Identification

Drug Identification can be found by UV spectroscopy, IR Spectroscopy.

UV Spectroscopy:-

A stock solution of Doxofylline 5 µg/ml was prepared separately in Water. The UV spectrum of Doxofylline was recorded using double beam UV-Visible Spectrophotometer (Shimadzu, UV-2450) at 1.0 cm slit width using 0.1 N HCl pH 1.2 as solvent in the range of 200-400nm. The wavelength of maximum absorption at 274 nm was found to be sharp and satisfactory.

FTIR of pure drug

Identification of Doxofylline was carried out using FTIR study. For this the FTIR spectra of plain drug was recorded in FTIR 8400 S Shimadzu spectrophotometer. The pure Doxofylline drug was mixed thoroughly with potassium bromide. For the scans were obtained at a resolution of 4000400cm^{-1}.

Calibration curve of Doxofylline in 0.1 N HCl

Solvent:- 0.1 N HCl pH 1.2

Concentration:- 5 µg/ml

(λmax=274.20 nm)

Stock solution was prepared by dissolving 50 mg drug in 100 ml simulated 0.1N HCL pH 1.2(500 µg/ml). From this solution withdraw 4 ml and make up simulated 0.1 N HCl buffer pH

1.2 up to 100 ml (20 µg/ml).

Withdraw 2.5,5,7.5,10,12.5 ml from stock solution and make upto 10 ml with simulated 0.1 N HCl pH 1.2 to produce solution of concentration 5,10,15,20 and 25 µg/ml respectively.

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Drug excipients compatibility study By FTIR

Compatibility of Doxofylline with the respective Polymers that is Hydroxypropyl Methyl Cellulose, Xanthan Gum, Guar Gum. Individual excipients was established by Infrared Absorption Spectral Analysis (FTIR). Any changes in the chemical composition after combining with the excipients were investigated with IR spectral analysis.

Formulation Table : Formulations Composition of Sustained Release Matrix Tablets of Trial Batches

Sr. No.	Ingredients (mg)	T1	T2	T3	T4	T5	T6
1	Doxofylline	400	400	400	400	400	400
2	HPMC K100M	200	---	---	100	100	---
3	Xanthan Gum	---	200	---	100	---	100
4	Guar Gum	---	---	200	---	100	100
5	Avicel 101	34	34	34	34	34	34
6	PVP K90D	6	6	6	6	6	6
7	Magnesium Stearate	5	5	5	5	5	5
8	Talc	5	5	5	5	5	5
9	IPA	q.s	q.s	q.s	q.s	q.s	q.s

Sr.No.	Ingredients	Quantity
1.	Doxofylline	400
2.	HPMC K100M	100
3.	Xanthan gum	100
4.	Gaur gum	100
5.	Avicel 101	34
6.	PVP K90D	6
7.	Magnesium Stearate	5
8.	Talc	5
9.	IPA	q.s

Evaluation of Matrix Tablets Pre compressional

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and 10 gm of sample powder was filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, was found by measuring in different direction. The height of the heap was measured by using scale.

Bulk density

A known quantity of powder was poured into the measuring cylinder carefully leave the powder without compacting, if necessary and read the unsettled apparent volume, to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula

Bulk density = Bulk Mass/ Bulk Volume

Tapped density

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder was mechanically tapped and volume readings are taken until little further volume changes were observed.

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Carr's Index

The compressibility index of all ingredients was determined by following equation. **Carr's index = (Tapped density-Bulk density/ Tapped density) ×100**

Hausner Ratio

Hausner predict the flow properties of powder by using inter particle friction. **Hausner ratio = tapped density /poured density**

Post compressional parameters Thickness and Diameter

Tablet thickness and Diameter was measured by Vernier caliper.

Hardness

The hardness is expressed as Kg/ cm2. The tablet crushing load, which is the force required to break a tablet into halves by compression .It was measured using a tablet hardness tester (Pfizer Hardness Tester).

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre-weighed sample of tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

Weight variation

USP weight variation test is done by weighing 20 tablets individually; calculating the average weight and comparing the individual tablet weight to the average weight variation tolerance.

***In vitro* dissolution study of matrix tablet.**

The release rate of Doxofylline sustained release matrix tablets was determined using USP type II dissolution apparatus. *In-vitro* dissolution study was carried out in 0.1 N HCl for 2 hours & in Phosphate buffer (pH 6.8) mimicking passage of dosage form from stomach to ileum. In order to simulate pH changes along the GI tract two dissolution media with pH 1.2 & 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 h (since the average gastric emptying time is 2 h), then removed and the fresh pH 6.8 Phosphate buffer was added. 900 ml of the dissolution medium was used each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5^{0}C. The sample were filtered through 0.45 µm nylon filter and spectrophotometrically analysed at 274 nm.

2. RESULTS AND DISCUSSION

Analysis of drug candidate Melting Point:-

Thus, it has been identified that Observed Melting Point of Doxofylline is within the Specific Range so it conform that Doxofylline drug is pure.

Drug identification

Determination of maximum wave length in 0.1 N HCl buffer pH 1.

From the UV spectroscopic analysis the maximum wavelength is found at 274.20 nm which is near to the standard reported value 274nm. Hence, 274.20 nm is taken as a maximum wavelength.

Determination of maximum wave length in Phosphate buffer pH 6.8

From the UV spectroscopic analysis the maximum wavelength is found at 273.60 nm which is near to the standard reported value 274nm. Hence, 273.60 nm is taken as a maximum wavelength.

FTIR characterization:

From the data shown in table 6.4 and figure 6.5, it was observed that the FTIR peaks of sample Doxofylline drug is nearly equal to the peaks reported for the standard Doxofylline drug. Therefore it can be concluded that the given sample is pure Doxofylline drug.

Evaluation of Matrix Tablet Pre compressional parameters

Flow property of granules for all formulated batches is shown in table no. 6.6. The bulk density varies between 0.41 to 0.51 gm/ml, the tapped density varied between 0.48 to 0.56 gm/ml, the Carr's index varies between 7.90 to 15.68 % and Hausner's ratio 1.08 to 1.18 %. Further, angle of repose 21.33 to 28.81 was found. So that prepared granules shows a good flow property.

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***In vitro* Drug Release study of Trial batches of Doxofylline matrix tablets**

In vitro drug release of matrix tablets was performed using two different dissolution medium i.e. in pH 1.2 acid buffer for initial 2h followed by pH 6.8 phosphate buffer for next 24h to mimicking passage of dosage form from stomach to ileum.. The result of drug release in different media is shown in Table. No 6.8. Results indicated that formulation T3 releases 83.59 % of drug in 12h. Formulation T1 and T2 releases 85.39% and 93.18% of drug in 15 h. Formulation T6 releases 89.01% of drug in 18 h. Formulation T5 releases 87.44% of drug in 21h. So that they did not match with the prefixed goal of the sustained the drug release for 24h. But in case of formulation T4 drug release was found to be 94.25% in 24h. This meet the prefixed criteria for sustained the drug release for 24h time period. So that it can be concluded that among the six formulations T1, T2, T3, T4, T5 and T6; formulation T4 was most suitable for sustained the drug release for 24h.So optimization of T4 batch was done by using 3^k factorial design.

Post compressional parameters of Factorial Batches

From table no. 6.10 it was seen that all tablets passes the weight variation test as per IP. Further the parameters like hardness and thickness meet the criteria. The low value of % friability indicated the mechanical stability of the formulation.

Data analysis of Y1 (T50%)

The observed value for T50% for all 9 batches varied from 11.09 to 17 hr. The result clearly indicates that Y1 is strongly affected by the independent variables selected for the study. The response (Y1) obtained at various levels of two independent variables were subjected to multiple regression to give a quadratic polynomial equation no. 1

3. CONCLUSION

From the results and discussion following conclusion were drawn:

The present investigation deals with the formulation and evaluation of sustained release matrix tablets of Doxofylline for asthma using polymers such as HPMC K100M, Xanthan Gum and Guar Gum. As per trial batches concluded that combination of HPMC K100M and Xanthan Gum were suitable as release rate controlling polymers for sustaining of drug release for 24 hrs. So thus Doxofylline could be successfully delivered to provide 24 hrs relief of asthmatic effect by design of a sustained release matrix formulation. The FTIR and DSC study showed no sign of incompatibility, thus concluding the selected polymers are likely to be suitable for preparation of sustained release matrix tablet. The formulation was optimized using a two factor, three level full factorial Design. The amount of independent variables HPMC K100M (X1) and Xanthan Gum (X2) showed a significant effect on the dependent variables T50% (Y1) and T80% (Y2). The quantitative effect of these factors at different levels was predicated by using polynomial equations. Linearity observed between the actual and predicted values of the response variables suggested the prognostic ability of the Response surface methodology design. Response surface methodology was the used to predict the levels of the factors X1 and X2 required to obtain an optimum formulation with good T50% and T80%. A optimized formulation was prepared according to these levels. From evaluation parameters of factorial batches it should be concluded that if the concentration of HPMC K100M and Xanthan Gum increase than T50% and T80% will be increase. After all evaluation of optimize batch was selected for the 1 month stability study and the result revealed that there is no significant change in drug release profile and physical parameters which indicates that the selected formulation is stable.

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