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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLET OF TRIMETAZIDINE DIHYDROCHLORIDE

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Abstract

The anti-hypertensive drugs will dominate the global cardiovascular market with a market share of nearly 50%.[1] A common problem associated with Trimetazidine dihydrochloride conventional therapy is that of "dose-dumping" or "dose loading" resulting in increased risk of toxicity. Conventional therapy is also associated with a high incidence of gastro intestinal side effects and seen in about 30% patients. However, a sustained release Trimetazidine dihydrochloride formulation will release a smaller amount of drug and hence ensure a decrease in side effects.

Keywords: - : Anti-hypertensive drugs, Trimetazidine dihydrochloride etc

Introduction

A sustained release Trimetazidine dihydrochloride matrix tablet formulation will be desirable from the viewpoint of patient comfort through reduction of side effects and for increasing the bioavailability of the drug. This work was an attempt to use a combination of natural hydrophilic polymer matrix and hydrophobic polymers for sustaining the Trimetazidine dihydrochloride release.

The objectives of this study were

1)To design sustained release dosage form for highly water soluble drug (i.e. Trimetazidine dihydrochloride).

2)To evaluate a combined Hydrophilic – Hydrophobic matrix system for sustaining the drug release of Trimetazidine dihydrochloride.

3)To study the effects of the following variables on the characteristics of Trimetazidine dihydrochloride sustained release matrix tablets:

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Formulation variables:

- Polymer concentration,Effect of coating.

♦ Process variables:

- Compression force,Dissolution medium.

Matrix tablets:[2,3]

A *matrix* is an inert solid vehicle in which a drug is uniformly suspended. A matrix may be formed by compressing the drug and the matrix material together. Most matrix materials are water insoluble, although some matrix materials may swell slowly in water .

Types of matrix tablet

Hydrophilic matrices 2)Hydrophobic matrices 3)Plastic matrices

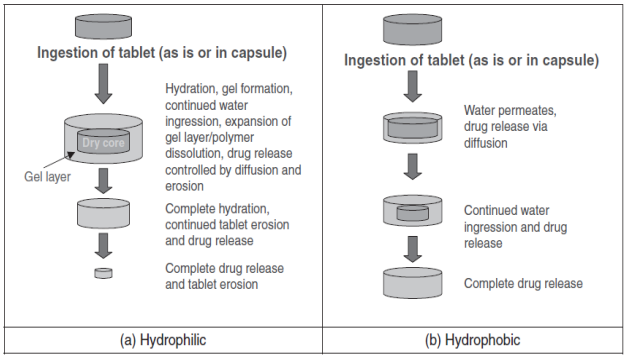

Fig. No. 1: Drug release process of hydrophilic and hydrophobic matrix systems

Formulation Code	Drug (mg)	Xanthan Gum (mg)	Ethyl Cellulose (mg) (High Viscosity)
T1	35	20	50
T2	35	20	60
T3	35	20	70
T4	35	30	50
T5	35	30	60
T6	35	30	70
T7	35	40	50
T8	35	40	60
T9	35	40	70

Table No. 1: Formulation of Trimetazidine Dihydrochloride SR tablets[4]

* (Each formulation contains 1% Magnesium stearate, 1% aerosil, 5% PVP paste in isopropyl alcohol (IPA) and Lactose is added to each formulation upto 200 mg

RESULTS AND DISCUSSION

Spectrophotometric characterization[5]

Preparation of calibration curve – (λ max determination)

The solution of Trimetazidine dihydrochloride was scanned for determination of λmax. UV spectrum of Trimetazidine dihydrochloride was found to be at 268.5nm in 0.1N HCl. and also The solution of Trimetazidine dihydrochloride was scanned for determination of λmax. UV spectrum of Trimetazidine dihydrochloride was found to be at 270 nm in phosphate buffer (pH 6.8).

FT-IR study

Infrared spectrum of Trimetazidine dihydrochloride was recorded. The observed peaks are match with the peaks given in pharmacopoeia which confirms that the supplied samples was of Trimetazidine dihydrochloride.

FORMULATION STUDIES[6]

- **Evaluation of precompression parameters of drug and excipients**

The prepared powder mixtures were evaluated for the blend property like bulk density, tapped density, Carr's index and angle of repose.

Formulation	Bulk Density (g/ml) (± SD)	Tapped Density (g/ml) (± SD)	Compressibility Index (%) (± SD)	Angle of Repose(º) (± SD)
T1	0.22±0.01	0.32±0.04	16.7±0.6	26.5±0.4
T2	0.23±0.03	0.29±0.02	17.6±0.7	23.6±0.7
T3	0.22±0.01	0.28±0.02	19±0.4	25.5±0.4
T4	0.25±0.02	0.3±0.03	18.4±0.6	24.6±0.6
T5	0.26±0.04	0.34±0.03	16±0.5	25±0.4
T6	0.24±0.03	0.31±0.04	19±0.3	23.8±0.8
T7	0.23±0.02	0.29±0.01	18.8±0.6	25.2±0.5
T8	0.25±0.04	0.35±0.04	17.7±0.6	23.6±0.5
T9	0.25±0.03	0.34±0.01	16.5±0.4	25±0.4

n=3

Table No. 2: - Blend properties of formulation of Trimetazidine dihydrochloride matrix tablets prepared by wet granulation method.

EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS

- **PHYSICOCHEMICAL PARAMETERS:-**

The prepared formulations were evaluated for the physical characteristics like thickness, hardness, friability and weight variation.

Formulation	Thickness[#]	Hardness (kg/cm^2) ± SD[*]	Friability (%)	Weight Variation (mg) ± SD[#]
T1	3.7±0.06	5.84±0.38	0.719	197.79±2.82
T2	3.45±0.05	5.76±0.32	0.687	203.05±5.29
T3	3.39±0.05	5.64±0.26	0.517	198.86±4.02
T4	3.63±0.04	5.82±0.28	0.451	199.16±3.12
T5	3.63±0.04	5.7±0.25	0.529	201.33±3.67
T6	3.75±0.04	6±0.22	0.403	202.68±4.58
T7	3.76±0.06	5.94±0.27	0.563	201.75±5.66
T8	3.63±0.03	5.92±0.16	0.438	197.42±4.11
T9	3.61±0.05	5.76±0.33	0.358	202.73±3.56

[*] (n=3) and [#] (n=10)

Table No.3 : Physical evaluation of Trimetazidine dihydrochloride sustained release matrix tablet

SWELLING BEHAVIOR OF TABLETS

The polymer in the matrix undergoes simultaneous swelling, dissolution and diffusion into the bulk medium resulting in erosion of the polymer. Swelling behavior of all the formulations were studied for 12 hrs at an interval of one hour.

Swelling index for all the nine formulations was studied. It showed that as the concentration of hydrophobic polymer increases, % swelling index decreases. Hence, formulations containing 30% of ethyl cellulose had more swelling index compared to formulations containing 35% of ethyl cellulose and formulations containing 25% ethyl cellulose had more swelling than all other formulations. All the formulations showed increase in swelling indices for 9-11 hrs. The matrices % swelling index increases at the beginning attains a maximum and then declines. The % swelling index for all the formulations are given below:

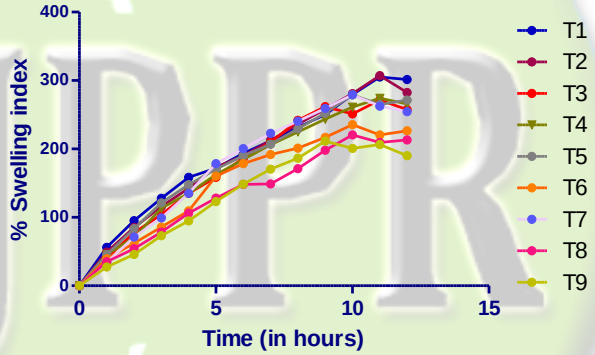

Figure no. 2 : Plot of % swelling index for T1 – T9

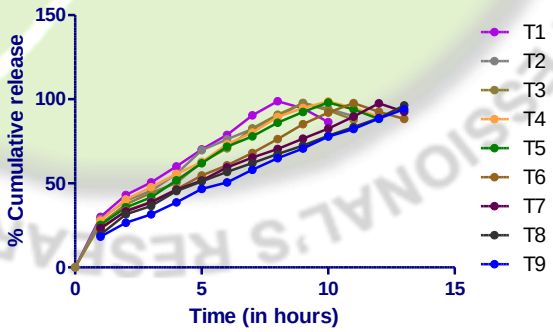

Figure No. 3: *In-vitro* dissolution profile of T1 – T9 formulation

STABILITY STUDY

Accelerated stability studies (AST) was carried for optimized batch T7 by exposing it to environmental condition like 40 °C/ 75%RH for one month. The sample was taken at different time interval i. e. 7, 14, 21, 28 and 45th day and analyzed for physical parameters like hardness, uniformity of content and percentage cumulative drug release.

SUMMARY AND CONCLUSION

The primary benefit of a sustained release preparation of Trimetazidine dihydrochloride is that a more uniform maintenance of blood plasma active concentration is achieved thus; potentially avoiding undesirable peaks. Therefore in the present study a sustained release formulation of Trimetazidine dihydrochloride is attempted.

It may be concluded from the present study that slow and sustained release of Trimetazidine dihydrochloride over a period of 12 hours was obtained (T1 to T9) by using hydrophilic polymer like Xanthan gum (10-20%) and hydrophobic polymer Ethyl cellulose (25-35%). It was successful in the formation of matrix and at the same time it is effective in retarding the drug release. Among all the formulation, T1 shows 98.78% in 8 hours and T9 shows that 94.04% at the end of 13 hours. The cumulative percentage drug release was decreased by increase in polymer concentrations of Xanthan gum and Ethyl cellulose. In summary, sustained release mechanism could achieve Trimetazidine dihydrochloride following oral administration without film coating. Developed sustained release dosage form are relatively inexpensive and easy to be manufactured by wet granulation technique.

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