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FORMULATION, DEVELOPMENT AND EVALUATION OF DOXOPHYLLINE SUSTAINED RELEASE MATRIX TABLET

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ABSTRACT
The study was done with an objective to achieve a potential sustained and controlled release oral drug delivery system of a antiasthmatic drug, doxophylline which having shorter half life. Hydroxypropyl methyl cellulose was used for gel forming agent. Differential scanning calorimeter (DSC) study show that drug and other excipints are compatible with each other. The tablets were evaluated for physical characteristic like hardness, weight variation, fraibilty, and thickness. It was found that drug release rate increased with the amount of osmogent because of the increased water uptake and hence increased driving force for drug release. Accelerated stability study was also performed for three months indicated that optimized formulation was stable. Use of HPMC as the total matrix material significantly influenced the release rate of the drug. Addition of different diluents like magnesium stearate and microcrystalline cellulose were used for improving flow ability and compressibility. Based on dissolution studies all the formulations showed sustained release of drugs from the formulations.
KEY WORDS: Doxophylline, Matrix Tablet, Sustained Release, Hydroxyl Methyl Cellulose, Avicel.

INTRODUCTION

By using oral controlled drug delivery system can provide continuous delivery of drugs at predictable and reproducible kinetics throughout the GI transit. Also the systems that target the drug delivery to a specific region within the GI tract for either local or systemic action[1]. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which are characteristic of the conventional intermittent dosage regimen[2].

Doxophylline [7-(1,3-dioxolane-2-methyl) theophylline], a new methylxenthine derivative which has ability to inhibit phosphodiesterase (PDE) and thus inhibit breakdown of cAMP (cyclic adenosine monophosphate). Increase in cyclic AMP inhibits activation of inflammatory cells in addition to bronchodilation. Doxofylline is rapidly absorbed and has high tissular diffusion due to its liposolubility. When administered orally the observed half-life is 7 ± 0.8 hours in adults. 90% percent is metabolized in the liver.

Among the various types of cellulose ether derivatives, HPMC polymers are popular in controlled release matrices due to their compatibility with numerous drugs[3,4]. HPMC is having the advantage that the material can go under direct compression of the drug blended drug with HPMC is easily accomplished[5]. The adjustment of the polymer concentration and the viscosity grade and the addition of different types and levels of excipients in the HPMC matrix can modify the drug release rate.

As the doxophylline is water soluble drug we can delay the release rate of drug by using matrix tablet. By this technique we can decrease the toxic effect of drug by controlling the loading dose[6].

MATERIALS AND METHODS

Materials

Doxophylline and hydroxyl propyl methylcellulose K-4M (HPMC K-4M) were received as a giftsamples from Yarrow Chem. India ltd, India. Microcrystalline cellulose, polyvinyl pyrolidone K-90 (PVP K-90) and magnesium stearate were generous gift samples from S.D. fine Chem.Ltd., Mumbai (India). All other chemical and reagent were of analytical grade and used as received.

Drug-excipients interaction studies

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of solid dosage form. Differential Scanning Calorimeter (DSC) allows the fast Evaluation of possible incompatibilities, because it shows changes in the appearance, Shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug doxophylline, other excipients and final tablet were recorded. (Fig. 1) The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50°C to 300°C[3].

Preparation of tablets

Six different formulations of matrix tablets (F1toF6) having a batch size of 100 tablets Containing doxophylline hydrochloride and other additives were prepared by wet granulation method in which the concentration of the drug was kept at 66.66% weight of the tablet (400mg /tablet) HPMC KM, HPMC K 100 and avicel in different proportions were used as polymers. Drug and polymers were passed through 60 # sieve and then dry blend of drug were granulated with PVP K-90 as a binder which was dissolved in isopropyl alcohol. The mass was dried at 50°C and sized through 22 # sieve. Finally, magnesium stearate were mixed as glidant, and then tablet blend was compressed rotary tablet compression machine (Rimek Tablet Machine, Minipress) using 16/32 mm, SC break line/plain. The tablet formulation is given in table 1. All the formulations were stored in the air tight container at room temperature for further evaluations[8,9].

POWDER FLOW PROPERTIES

(Table 2)

Angle of repose

The angle of repose of the mixture of the drug and excipients was determined by fixed funnel method. The values are used in the following equation to get the angle of repose.

$\tan \theta = h/r$

Where, h, r and θ are the height, radius and angle of repose of the powder pile[10,11,12].

Bulk density

Accurately weighed 3 g of the sample was transferred to the measuring cylinder of bulk density apparatus. The apparatus was adjusted for 100 tapping and noted the final volume as tapped volume.

Tapped density (ρt) = Weight of the powder / Tapped volume of the powder

Porosity

Porosity of the powder was determined by using formula:

Porosity = [(Vb – Vp)/ Vb] ×100.

Where Vb is the bulk volume and Vp is the true volume.

Carr's index

The carr's index of the powder was determined by using formula:

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Where, TBD is the total bulk density and LBD is the loose bulk density.

EVALUATION OF TABLETS

(Table 3)

Prepared tablets were evaluated for certain physical properties like uniformity of weight, hardness, friability and dissolution study etc.

Thickness

Thickness of the prepared matrix tablets were measured by using screw gauge. Ten tablets from each formulation were randomly selected and used. Thickness is expressed in millimeters.

Hardness

The hardness of the matrix tablets were measured using diametric compression using a hardness tester (Monsanto Type).. Six tablets from each formulation were randomly selected and used. The average hardness and the standard deviation were calculated. It is expressed in Kg/cm2.

Friability

Friability of the matrix tablets were determined. 10 tablets were randomly selected, weighed and placed in the Roche Friabilator. The apparatus was rotated at 25 rpm for 4 min. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% \text{ Friability} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Weight uniformity

Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.[7]

Accelerated stability studies

Optimized formulation were packed in blister and stored in ICH certified stability chambers maintained at 40°C and 75% RH for three months. The tablets were withdrawn periodically and evaluated for drug content and release studies.

***In-vitro* dissolution study**

In vitro drug release studies from the prepared matrix tablets were conducted for a period of 12 hours using a six station USP XXII type 1 apparatus at 37 ± 0.5°C and 50 rpm speed. The dissolution studies were carried out in triplicate for 12 hours (initial 2 hours in simulated gastric fluid and rest 10 hours in phosphate buffer of pH 6.8). At every 1-hour interval, samples of 10 ml were withdrawn from the dissolution medium and replaced with fresh dissolution medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed for doxophylline by an UV spectrophotometer at 275 nm (Shimadzu, Japan). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from doxophylline reference standard. Drug dissolved at specified time periods was plotted as percent release versus time (hours) curve[10].

RESULT AND DISCUSSION

Differential Scanning Calorimetry (DSC) Analysis

In order to investigate the possible physical interaction between drug and excipients, DSC studies were carried out. DSC curves obtained for pure doxophylline, HPMC K-4M, HPMC K-100M, PVP K-90, Avicel, Mg. stearate and their physical mixtures are shown in Fig. 1. Pure powdered doxophylline showed a melting endotherm at 144.56˚C. DSC scan of HPMC K-4M showed single broad endotherm at 109.93˚C due to melting whereas during scanning of HPMC K-100M, a broad endotherm ranging from 89.56°C was observed. DSC thermo grams of physical mixture of drug and excipients showed the melting peak of the drug at 143.50°C and broad endothermic peak at 122.58˚C due to melting of HPMC. Physical mixture of all above ingredients showed their identical peaks at defined temperature range. Presence of all peaks indicates that all ingredients are compatible with each other and THP forms matrix with HPMC K-4M and HPMC K-100M.

Powder flow properties

The results of preformulation parameters for formulated physical mixtures of all batches are shown in table 2. The flowability of the polymers was found to be quite good according to the flow properties. Angle of repose ranges from 20.18 to 29.39°, bulk density ranges from 0.310 to 0.381 g/cm3, % Compressibility ranges from 12.93 to 14.10%.

Physicochemical properties

The physicochemical properties of the formulated batches are shown in the table 3. The hardness of the matrix tables was found in the range of 7.20-8.6 kg/cm^2. Thickness ranges from 3.28-3.96 mm, friability ranges from 0.351-0.589 while the weight of the tables ranges 599-603mg/tablet.

***In vitro* dissolution study**

Dissolution study of the prepared doxophylline matrix tablet was carried out for 12 hours.(Fig. 2 and 3) From the release profile we can see that batches F1 to F6 shows release of drug more than 15% at first hour. The % drug release after 12 hours for formulation F1, F3, F4 was found to be 84.62, 94.58 and 89.6.85 respectively.

Accelerated stability study of best batch (F3)

Stability study was carried out for 3 months. sample withdraws at the interval of one month for three months which showed no change in *in-vitro* drug release profile (fig 4). Percentage assay cumulative release of drug shows 99.89 (initial), 98.51 (after 1 month). 97.36 (after 3months). From the result of the stability study we can conclude that the doxophylline matrix tablet is stable and shows no change at 40˚C for extended period of time.

CONCLUSION

Doxophylline sustained release matrix tablet was prepared successfully using HPMC as polymer to retard release and achieve required dissolution profile From DSC study, we can show that there is no change in drug's melting peak (144.56°C) after the preparation of tablet. Stability study of batch F3 after three month showed no change in in-vitro drug release profile. Hence, the optimized formulations seem to be stable. Based on dissolution studies all the formulations showed sustained release of drugs from the formulations. As expected the release rate was slower with higher viscosities of HPMC. The molecular weight variations in HPMC are commonly expressed as viscosity grades. Larger viscosity grades correspond to greater polymer molecular weight. Based on above studies it can be concluded that developed matrix formulation can serve as a successful sustained drug delivery system.

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Table 1: formulation of doxophylline matrix tablet

INGREDIENTS	FORMULATION CODE					
	F1	F2	F3	F4	F5	F6
Doxophylline	400	400	400	400	400	400
HPMC K-4M	25	-	50	-	55	40
HPMC K-100M	-	25	-	50	40	40
PVP K-90	15	15	15	15	15	15
MCC(Avicel)	150	150	125	125	95	105
Magnesium stearate	10	10	10	10	10	10

Total weight of each tablet = 600mg

Table 2: Powder flow properties for formulated physical mixtures

Formulation code	Angle of repose* (°)	Bulk density* (g/cm^3)	Porosity* (%)	Carr's index* (%)
F1	24.85±0.25	0.338±0.005	11.88±0.02	13.14±0.20
F2	20.18±0.19	0.374±0.007	12.14±0.08	12.93±0.78
F3	28.15±0.27	0.366±0.002	12.39±0.09	13.13±0.46
F4	21.58±0.52	0.370±0.001	13.25±0.07	13.80±0.88
F5	29.39±0.98	0.310±0.008	12.75±0.05	14.50±0.29
F6	26.48±0.20	0.381±0.002	13.45±0.05	14.90±0.25

Note: (*) All values are the mean of three readings

Table 3: Physicochemical parameters of developed matrix tablets of doxophylline

Formulation code	Hardness* (kg/cm^2)	Thickness* (mm)	Friability* (%)	Weight* (mg)
F1	7.20±0.140	3.91±0.001	0.351	601±1.00
F2	7.50±0.550	3.88±0.004	0.456	602±1.80
F3	8.03±0.120	3.56±0.006	0.421	601±2.30
F4	8.18±0.497	3.28±0.005	0.537	599±1.90
F5	8.60±0.290	3.75±0.003	0.467	603±0.80
F6	8.10±0.107	3.96±0.008	0.589	602±2.50

Note: (*) All values are the mean of three readings

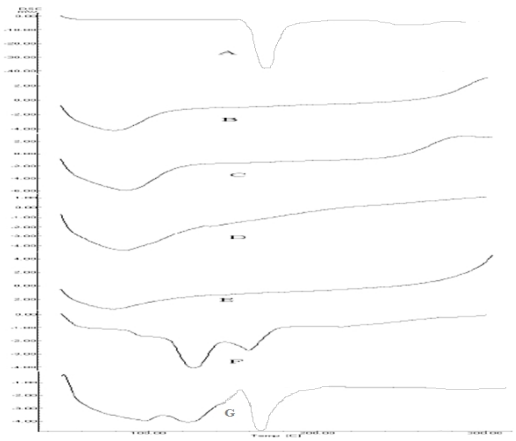

Fig. 1 : DSC Spectra of Doxophylline (A), HPMC K-4M (B), HPMC K-100M (C), PVP K 90(D), Avicel (E), magnesium stearate (F) & physical mixture of doxophylline with formulation excipients (G)

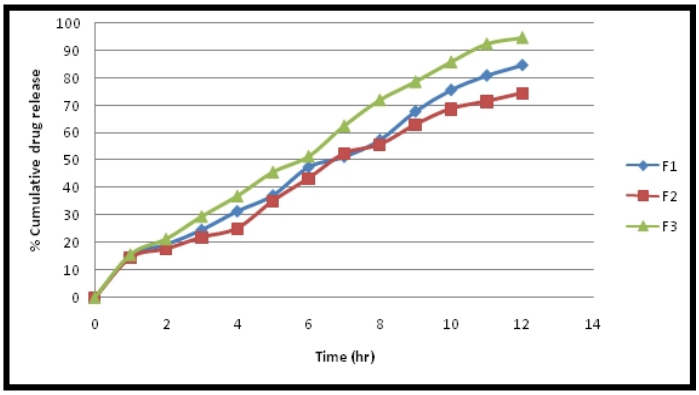

Fig. 2: *In-vitro* dissolution profiles release of batches F1 to F3

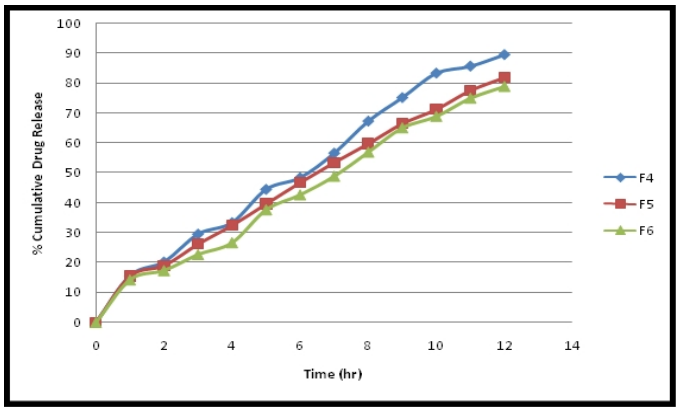

Fig. 3: *In-vitro* dissolution profiles release of batches F4 to F6

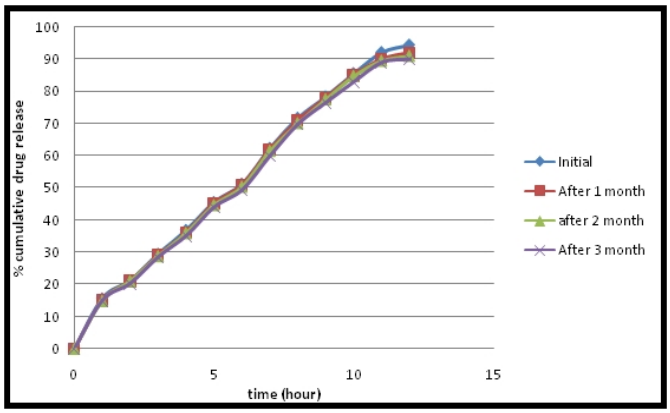

Fig. 4 : Drug release profile of THP SR matrix tablet before and after stability study of best batch F3

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