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Formulation and Evaluation of oral controlled release matrix tablets of Paroxetine

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ABSTRACT

The purpose of the present study was to formulate and evaluate oral extended release matrix tablets of Paroxatine using hydroxy propyl methylcellulose (HPMC) and polyethylene oxide (PEO) as the release rate retardant polymers. The study includes in vitro characterization of tablets such as physico chemical properties, in vitro dissolution, DSC and FTIR. Selected formulations based on the in-vitro drug release study were packed in HDPE containers and kept for accelerated stability condition at 40°C and 75 % relative humidity. In vitro release studies revealed that the release rate decreased with increase in polymer concentration, polymer viscosity. In-vitro release kinetics indicated that the drug release from the matrix tablets was followed first order kinetics with diffusion mechanism. Results of Differential scanning calorimetry (DSC) and Fourier Transforms Infrared Radiation measurement (FT-IR) of initial and stability samples have shown that there was no incompatibility observed between the drug and excipients used in the formulation of matrix tablets. The developed controlled release matrix tablets of were stable up to three months. The release rate of the matrix tablets for prolonged periods of time can be advantageous than conventional Paroxatine tablets.

Key words: Paroxatine, matrix tablets, controlled release, stability, DSC, FTIR.

1. INTRODUCTION

Extended release is a kind of controlled release system that provides the medication for prolonged periods of time [1]. Oral route is the most popular route of drug administration because of its ease of administration and patient compliance [2]. Even though oral route is preferred by the patients, in case of chronic situations the dosage form should be administered in divided doses for longer periods of time and again this is a non compliance to patients. There are several disadvantages if the drug is administered frequently [3]. Dose modification is required in such situations [4]. Extended release (XR) formulations are preferred because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety [5].

Paroxetine hydrochloride is a phenylpiperidine antidepressant agent which selectively inhibits serotonin reuptake (SSRI) [6]. Paroxetine hydrochloride is heavily prescribed drugs and effective in patients with various psychiatric disorders. However, there were adverse effects associated with SSRI. Certain adverse effects are thought to be linked to increased serotonin in the CNS (e.g. sexual dysfunction and somnolence) and periphery [7]. To decrease these adverse effects of paroxetine hydrochloride upon oral administration, the development of controlled release delivery system is required, that can maintain therapeutic drug levels for a longer period of time [8].

Hydrophilic polymers are commonly used as rate-controlling polymers for extended release matrix-type dosage forms. Hydroxy propyl methyl cellulose (HPMC) is a hydrophilic polymer used in the matrix type systems for the prolonged drug release. HPMC matrix tablets may be affected by several formulation variables, such as polymer concentration [9] molecular weigh [10] drug levels and solubility [11], type of excepient and tablet shape and size [12]. The Hydrophilic polymer matrix swells as water diffuses into the tablet. Usually HPMC upon contact with aqueous media begin to hydrate, swell, coalesce, and form a viscous phase around the surface of the tablet. For hydrophilic matrix tablets comprised of water-soluble, swellable polymers such as HPMC, the release kinetics are described by drug diffusion and polymer dissolution, i.e surface erosion. Drug release is dependent on the relative contribution of diffusion and erosion release mechanisms [13]. The matrix geometry is also one of the important factors for drug releases from extended-release dosage forms [14]. Specifically for HPMC matrix tablets, the effect of matrix geometry on drug release has also been studied in detail [15]. Poly

(ethylene oxide) (PEO) is a hydrophilic polymeric excipient that can be used in formulations for different purposes [16]. PEO s are mostly used to produce controlled release solid dosage forms such as matrices, reservoirs, or coated cores. Due to their chemical structure, in the presence of water, control the release of the active moiety either by swelling or by eroding and swelling forming a hydrogel. In both cases, the water triggers the process starting the erosion and/or the swelling processes. PEO has been used in association with HPMC to delay the release of a drug by controlling the extent and rate of swelling of the polymers [17].

However, there appears a limited literature available on XR formulations of Paroxatine. The purpose of this study was to design oral XR tablet formulations of Paroxatine using HPMC and PEO as the retarding polymer. The tablets were formulated by direct compression method, and their physical and in vitro release characteristics were evaluated. The effect of formulation factors such as polymer proportion, polymer type on the release characteristics was studied in order to optimize the formulation.

2. MATERIALS AND METHODS

Paroxatine was obtained as a gift sample from Alkem laboratories Ltd (Mumbai, India). Hydroxypropyl methylcellulose (HPMC K 100 M) were obtained from Colorcon Asia Private Ltd , Poly (ethylene oxide) (Polyox WSR 303) was obtained from The DOW Chemical Company, Micro crystalline cellulose (Avicel PH 200) was obtained form FMC Biopolymers, USA, colloidal silicon dioxide (Aerosil) was obtained form Degussa, Germany, talc was obtained form Luzenac, France and magnesium stearate was obtained form Ferro Industrial Chemicals USA. All other chemicals and reagents used in the study were of analytical grade.

2.1 Analytical method

Validated UV Spectrophotometric method was used for the determination of Paroxatine using Schimadzu, UV-1700 E 23 in pH 7.2 tris phosphate buffer at 290 nm.

2.2. Formulation of Paroxatine matrix tablets

Matrix tablets of Paroxatine were prepared using various proportions of HPMC and PEO as the retarding polymer. The tablets were manufactured by the direct compression. The drug, polymer(s) and all other excipients sifted through 425 μm sieve (ASTM mesh no 40) and mixed uniformly. The dry mix blend was mixed with aerosil and talc followed by magnesium stearate. The lubricated granules were characterized for drug content. The lubricated granules were directly compressed on 16-station tablet compression machine using 7 mm flat faced round (FFR) punch. (Cadmach Machinery Co, Ahmedabad, India). Three batches were prepared for each formulation and compressed in to tablets form each batch for the characterization study.

2.3. Characterization of the Designed Tablets

2.3.1. Drug content estimation

The drug content of the prepared matrix tablets was determined in triplicate. For each batch, 20 tablets were taken, weighed, and finely powdered. An accurately weighed 150 mg of this powder was taken and suitably dissolved under sonication (Power sonic 505, HWASHIN technology co) in pH 7.2 tris phosphate buffer and filtered through 0.45 μ (Millipore) filter. The sample was analyzed after making appropriate dilutions using UV spectrophotometer (Schimadzu, UV-1700 E 23) at 290 nm against blank.

2.3.2. Hardness, weight variation and friability determination

The weight variation was determined by taking 20 tablets using an electronic balance (type ER182A, Mettler Toledo). Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics) for 300 revolutions at 25 rpm.

2.3.3. In Vitro Drug Release Studies

The in vitro dissolution studies were performed for the prepared tablets using dissolution apparatus (LABINDIA, DISSO-2000, Mumbai, India).. The dissolution medium consisted of pH 7.2 tris phosphate buffer (900 mL), 150 rpm speed, maintained at 37 ±0.5 °C. The samples were with drawn at different time intervals and evaluated by using UV spectrophotometer as per the method specified in the method section.

2.3.4. Fourier transforms infrared radiation measurement (FT-IR)

The FT-IR spectra acquired were taken from dried samples. A FT-IR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 and 400 cm-1, with 4 cm-1 resolution. A quantity equivalent to 2 mg of pure drug and matrix tablets were selected separately.

2.3.5 Differential scanning calorimetry (DSC) study

Differential scanning calorimetry (DSC) study of matrix tablets was performed using a Diamond DSC (Mettler Star SW 8.10) to determine the drug excepient compatibility study. The analysis was performed at a rate 5 0 C min -1 from 500 ^{O}C to 2000 ^{O}C temperature range under nitrogen flow of 25 ml min -1.

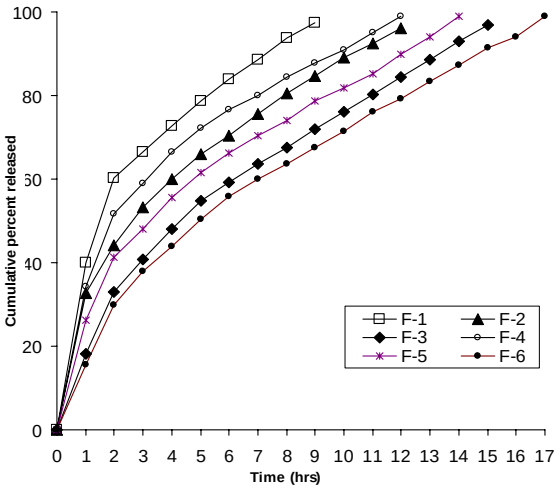
Table -1: Formulation and physical characteristics of designed controlled release matrix tablets of Paroxatine

Formulation	F-1	F-2	F-3	F-4	F-5	F-6
Components	mg per tablet					
Lamivudine	25	25	25	25	25	25
HPMC K 100 M	25	35	45	-	-	-
PEO WSR 303	-	-	-	25	35	45
MCC	60	50	40	60	50	40
Aerosil	6	6	6	6	6	6
Talc	4	4	4	4	4	4
Mg stearate	1	1	1	1	1	1
Total weight	120	120	120	120	120	120
	Physical/ chemical Properties					
Drug content (%)	99.815	100.85	100.5	99.86	99.5	100.3
Hardness (kg/cm²)	6.5 (±0.3)	6.2 (±0.4)	6.4 (±0.4)	6.1 (±0.3)	6.2 (±0.3)	6.5 (±0.1)
Thickness (mm)	3.60	3.55	3.61	3.53	3.6	3.57
Friability (%)	0.6	0.5	0.5	0.65	0.6	0.7
Zero order	0.9971	0.9934	0.9841	0.9932	0.9911	0.9891
First order	0.9421	0.9011	0.9435	0.9265	0.9038	0.9667
Higuch	0.9018	0.9321	0.9693	0.9414	0.9458	0.9568

3. RESULTS AND DISCUSSION

Prepared tablets were evaluated to weight variation study. The results of weight variation test are shown in the Table 1 and the values are around 120 mg. The tablets thickness of the prepared formulations was observed in the range of 3.5mm to 3.6 mm. The hardness of all the tablets was found to be in the range of 6 kg/cm². The friability of the prepared tablets was below 1% clearly indicates the good mechanical strength of the tablets.. The drug content ranged from 99.82 to 100.85 in formulation clearly indicating good content uniformity. The formulations were summarized in Table 1. The in vitro dissolution study showed that the drug release was extended up to 18 hours. The release for the formulations prepared with HPMC K 100 M was faster when compared with the tablets prepared with Polyethylene oxide (PEO), The mainly depends up on the polymer type and the polymer concentration. The release kinetics form the dissolution data was followed zero order release with diffusion mechanism. Table 1 shows the release kinetics of the prepared paroxatine matrix tablets.

Figure -1: Cumulative percent drug release vs time plot of Paroxatine tablets



Differential scanning calorimetry (DSC) study of pure Paroxatine showed a sharp endothermic peak at 132.5° C. The thermograms of Paroxatine matrix tablets showed similar endothermic peak at 132° C. This further confirms that there is no drug to polymer interaction. This was further conformed by FTIR

Figure -2: DSC thermogram of (A) pure Paroxatine (B) Paroxatine matrix tablets prepared with HPMC (C) Paroxatine matrix tablets prepared with PEO.

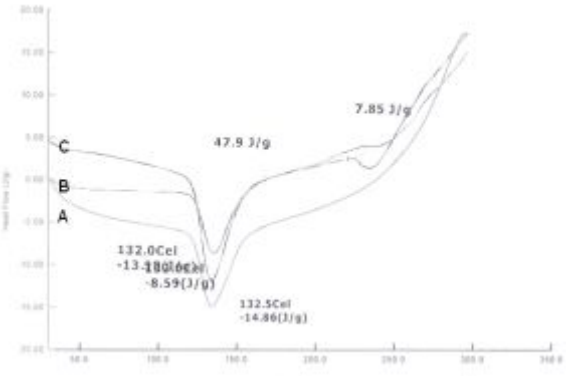
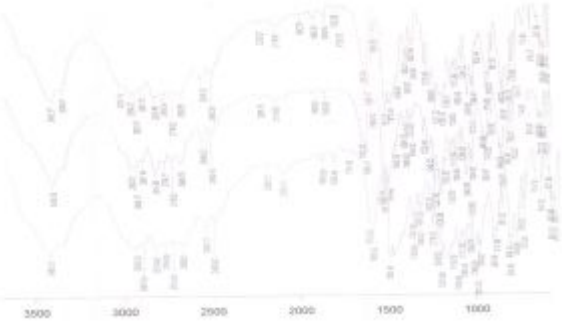


Figure -3: FTIR Spectrum of (A) pure Paroxatine (B) Paroxatine matrix tablets prepared with HPMC (C) Paroxatine matrix tablets prepared with PEO.



4. CONCLUSION

Matrix tablets of Paroxatine were prepared by direct compression method. DSC and FTIR study shows no drug polymer interaction. The prepared formulations have potential commercial applications.

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