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STUDIES ON WATER SOLUBLE HPMC GRADES FOR THE DEVELOPMENT OF PAROXETINE HYDROCHLORIDE ORAL FILM

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ABSTRACT The main objective of the present study was to compare the two grades of water soluble HPMC in the development of Paroxetine hydrochloride oral film. Taste mask complex of a paroxetine and mannitol was prepared using solvent evaporation method.The FTIR, DSC and TLC studies demonstrated no interaction in between Paroxetine hydrochloride, HPMC E5 and HPMC E50.The prepared films (F1-F8) were analysed for physical appearance, weight variation, thickness, tensile strength, folding endurance, drug content, disintegration and dissolution parameters. HPMC E5 showed better results for fast drug dissolution, and disintegration, while HPMC E50 showed better results for tensile strength and folding endurance at comparable and varying concentration range 4.5 %, 3.5%,2.5% ,1.5%.The better results of folding endurance, dissolution time, disintegration time and tensile strength suggested F2 formulation as better developed film which contains HPMC E5 (2.5%). The mouth dissolving film of Paroxetine hydrochloride was formulated with HPMC water-soluble E-5 gradedisintegrates within few seconds and releases drug rapidly to give its therapeutic effect. Low viscosity and better hydrophobicity with film forming ability of HPMC E5 confirm the suitability for preparation of oral mouth dissolving films for fast onset of action. The present study revealed that formulated paroxetine hydrochloride mouth dissolving film with E-5 grade has better oral film properties than HPMC E50.

KEYWORDS : Paroxetine Hydrochloride, Hpmc E 5, Hpmc E 50, Oral Film.

INTRODUCTION

Late onset of action and difficulty in swallowing are the major drawbacks of conventional drug delivery systems.[1] It is well known that administration of drugs through oral mouth cavity is the best solution for fast onset of action and better bioavailability [2]. Within fraction of seconds of time drug starts absorption and pharmacological effects observed [3] . Oral Fast dissolving films dissolves in mouth cavity and shows absorption of drug through oral cavity mucosa via buccal site and sublingual site[4].

Depression is such a disease, in which patient can do suicidal thinking or any unwanted act if drugs not get in time.Depression seems to be a very common disorder in all over the world, millions of peoples are affected by depression. Depression is unlike usual mood swings or temporary emotional reactions to daily problems. Near about millions of deaths occurs in each year due to depression.[5] Paroxetine hydrochloride is a very potent and selective serotonin reuptake inhibitor (SSRI) used in the treatment of the major depressive disorder, panic disorder, social anxiety disorder, posttraumatic stress disorder, obsessive-compulsive disorder (OCD)[6]. Paroxetine hydrochloride is a highly water soluble and highly membrane permeableBCS class-I drug. It has once a day dosage with elimination half-life approximately 21 hrs. Paroxetine hydrochloride shows very good absorption by oral route but gets highly metabolised by the first-pass metabolism in liver results in poor oral bioavailability of 31± 15%.[7]

Formulation of mouth dissolving film of Paroxetine hydrochloride has been done with the objective to increase bioavailability of Paroxetine hydrochloride by avoiding extensive first-pass hepatic metabolism and to give better patient compliance, especially within geriatric, paediatric patients also in patients which suffering from nausea, vomiting, motion sickness[8].Mouthdissolving film increases the efficacy of drug by dissolving in the oral cavity within a fewseconds.Fast oral dissolving films provide better patients compliance and fast onset of action as compared with the conventional oral dosage form. Mouth dissolving film is a very good alternative to conventional oral dosage forms.[9]

HPMC E5 and HPMC E50 are widely used water soluble film formers in the design and development of oral films. Their film forming properties should be compared to select the better polymer to design and develop oral film drug delivery of Paroxetine hydrochloride [10].

MATERIALS

Paroxetine hydrochloride was obtained from Balaji Drugs, Gujarat. HPMC E 5 and HPMC E 50 were obtained as a gift sample from colorcon Pvt, Ltd., Verna Goa. Propylene glycol was obtained from Pallav chemicals and solvents Pvt. Ltd., Nashik. Analytical and pharmaceutical grade materials, chemicals and reagents were used for the present study.

METHODS

Preparation of Paroxetine hydrochloride loaded oral films

Formulations of oral mouth dissolving films were prepared and are shown in table 1. The weighed quantity of HPMC E5 or HPMC E50 (1.5 to 4.5 %) was taken and kept for soaking in distilled water for overnight with constant shaking. Next day polymer solution was stirred on a magnetic stirrer for 2 hrs.[9]

In another beaker accurately weighed Paroxetine hydrochloride, citric acid and sodium saccharine was taken and dissolved in sufficient quantity of water. Further, drug solution and the polymeric solutions of HPMC E5 or HPMC E50 (1.5 to 4.5 %) mixed separately and stirred to get a homogenous solution then kept aside to remove air bubbles. During stirring 4 ml propylene glycol was added as a plasticizer.[10] The final solution was cast on a 9 cm diameter petri dish which was previously lubricated with glycerine then kept in an oven at 60^0C for drying. After drying the films were carefully removed and cut into 2×2 cm^2 size. The good quality films were wrapped with aluminium foil and stored in tightly closed container and placed at dry place.[11]

EVALUATION OF MOUTH DISSOLVING ORAL FILMS

Physical appearance and surface morphology

Physical appearance and morphology studied by visual examination of films and by use of scanning electron microscopy (SEM). The sample was put in the SEMs sample slab. The sample was coated with gold as conducting material (200A^0)under reduced pressure of about0.001 Torr for 5 min to increase the conductivity using an Ion beam sputtering system device (JEOL, JSM 5610).[12,13]

FTIR study

The infrared spectrums of Paroxetine hydrochloride (pure drug), physical mixture of drug with HPMC E5, drug with HPMC E50 were recorded by using FTIR (Agilent Cary 630). The identified peaks of the reported IR spectrum of Paroxetine hydrochloride and sample werestudied for the drug excipient compatibility. [14]

Differential scanning calorimetry (DSC) study

Thermograms of pure Paroxetine hydrochloride and physical mixture of drug with excipients were accomplished by the use of differential scanning calorimeter (TA-60 WSI, Shimadzu, Tokyo, Japan). Samples were mounted in the sealed flat-bottom pan. Then the pan was put in DSC instrument and scanned between 30 and 300^{0}C at a rate 10^{0}C per minute. The carrier gas used was nitrogen (dry) to avoid oxidative and pyrolytic reactions with a rate of 10ml/min. Compatibility of drug with other excipients was studied.[14]

Thin layer chromatography (TLC) study

Thin layer chromatography of Paroxetine hydrochloride drug (standard) and physical mixture of drug excipients was performed. Thesilica gel precoatedTLC splates were use. Samples spots were given at base line of plate. Ethyl acetate: acetic acid: water (7.5:1.5:1) was used as mobile phase. The spot was located by fluorescence.Rf value was noted.[12]

Weight variation study

The weight variation study of the mouth dissolving films carried out by cutting the film of size 2×2 cm^2 from three different places of the casted film. The weight of each individual film was measured on digital balance and weight variation studied.

Thickness

Thickness uniformity of the films indicates dose accuracy in the films. Thickness was measured by using a digital Vernier calliper instrument. The thickness at three different places of one casted film was measured and mean with standard deviation was calculated.

Surface pH

For this study film was kept in a petri dish then 5 ml distilled water was added on surface film after 1 hr pH meter electrodes were brought in contact with the surface of the moistened film and pH readings were taken.[14]

Folding endurance

Folding endurance was calculated by folding the film of size 2×2 cm^2 repeatedly at the same place until the film breaks. The number of folding the film without breaking was noted down as a value of folding endurance.[15]

Tensile strength

Tensile strength was determined by applying maximum load to a point at which film get breaks. It is calculated by formula i.e. load applied at a breaking point of film divided by the cross-sectional area of the strip (g/cm^2).[16]

Percentage elongation

It was calculated by taking a difference between the final length of film (after elongation) and the initial length of the film (before elongation) divided by the initial length of the film.

Drug content

Drug content of formulated mouth dissolving films was determined by cutting the film of size 2×2 cm^2 from three different places of the casted film. Each individual film dissolved in 50 ml of phosphate buffer of pH 6.8 with stirring on the magnetic stirrer. Then the individual solution was filtered through *Whatman* filter paper later suitable dilutions were made and absorbance was measured at 293 nm. % Drug content present in the oral film was determined. Then average and standard deviation were calculated.[18]

***In-vitro* disintegration study**

In-vitro disintegration time of the film was measured by keeping the film in a petri dish containing 15 ml of phosphate buffer of pH 6.8 and swirling. The time taken by the film to disintegrate completely was noted as *in vitro* disintegration time.[19,20]

***In vitro* dissolution study**

In vitro dissolution study on formulated films was performed using USP type I basket type apparatus. To carry out this study 300ml phosphate buffer of pH 6.8 was used as dissolution media, the temperature was maintained at 37^{0}C ± 0.5^{0}C at 50 rpm. The film of size 2×2 cm^2 was placed into a basket and immersed in dissolution fluid. Samples of 1ml were withdrawn at the intervals i.e. 0.30 sec,1,2,4,8,10,12,15 min respectively and sample solution was replaced with a fresh solution of phosphate buffer of pH 6.8 to maintain a constant volume. The withdrawn samples were filtered and the concentration of drug was determined by using UV-visible spectrophotometer at 293 nm.[11,21]

***Ex vivo* permeation study**

Ex vivo permeation study was performed by use of *Franz* diffusion cell and porcine oral mucosa. The receptor compartment of this cell was filled up with 15 ml phosphate buffer of pH 6.8 and the small magnetic bead was added into this receptor compartment oral porcine mucosa was mounted. The best-formulated film (F2) of dimension 2×2 cm^2 was placed on the upper surface of oral porcine mucosa then donor compartment was fixed on this by use of clamps. The whole assembly was placed over magnetic stirrer at a temperature 37±2^{0}C maintained through water jacket of the diffusion cell. The donor compartment was filled up with 1 ml phosphate buffer of pH 6.8 then samples of 1 ml were withdrawn at intervals of 2,4,6,8,10,15,20,30,40,50,60 minutes respectively same replaced with fresh phosphate buffer of pH 6.8. The sample solution was filtered by using *whatman* filter paper and analyzed on UV-Visible spectrophotometer at wavelength 293 nm.[11]

RESULTS AND DISCUSSION

In the present study, eight formulations of mouth dissolving films of Paroxetine hydrochloride were formulated using HPMC E 5 and HPMC E 50 as film-forming polymers. All the formulated films (F1-F8) showed good visible appearance and uniform consistency. The surface morphology by scanning electron microscopy (SEM) shown no any flaws or imperfection(figure 7).The all prepared films were subjected to weight and thickness study.Weight variation of prepared films from F1 to F8 varies from 35.62±2.35 to 72.01 ± 2.24 mg and Thickness varies from 0.12±0.005 to 0.23±0.014 mm showed good uniformity in weight and thickness. HPMC E 50 polymer containing films showed more weight and thickness over films containing HPMC E-5 as a film-forming polymer.The results were given in table 2.

FTIR Spectroscopy was studied to assure the compatibility of Paroxetinehydrochloride with polymers. The results were depicted in figure 1 and figure 2.The FTIR spectra showed compatibility between drug and polymers.

Figure 1: FTIR spectrum of Physical mixture of Paroxetine hydrochloride and HPMC E 5

Figure2: FTIR spectrum ofPhysical mixture of Paroxetine hydrochloride and HPMC E 50

DSC spectra showed peaks at 193.14^{0}C for paroxetine hydrochloride and at 189.98^{0}C for the physical mixture. It indicated that there was very little shift in melting peaks indicated no interaction between drug and excipients. The sharp peak indicated crystalline nature of drug. Results are shown in figure 3and figure 4. The TLC study of standard drug Paroxetine hydrochloride and the physical mixture sample carried out.Both TLC Results were showed no physical and chemical interaction of Paroxetine hydrochloride with excipients with constant Rf value 0.67. The results are shown in figure 8.

This study revealed that folding endurance increases with an increase in polymer concentration from 1.5 to 4.5% in both HPMC grades. HPMC E-50 polymer containing film having more folding endurance as compared to films containing HPMC E-5 polymer The result of folding endurance are shown in table 2.

The surface pH of all prepared films was found to be neutral in the range of 6.50-6.83. It indicated that the prepared films may not cause any potential irritation to the oral mucosa. The results are given in table 2.

The results were obtained from tensile strength and percentage elongation study of all formulated films showed the good flexibility and mechanical strength of films.HPMC E50 was found to be betterin tensile strength and percentage elongation as compared to HPMC E 5 as a film-forming polymer. The results are given in table 3.The prepared formulations were analyzed for its drug content uniformity and it was observed that all the drug content uniformity values lies between 98.6±2.56 to 99.6±3.03 %**.** The per cent drug content results are shown in table 3.

The *in-vitro* disintegration time of all formulated films was found to be in the range of 12.05±1.01 to 58.83±3.03 seconds which was satisfactory. The present study showed that disintegration time

increases with an increase in polymer concentration. The disintegration time of films containing HPMC E-5 is a film-forming polymer was found to be less as compared to HPMC E-50 as a film-forming polymer.As concentration of both polymers increased, disintegration time increased. The results are given in table 3.

In vitro drug release study revealed that drug release from formulated films containing HPMC E 5 as a film-forming polymer was more as compared with formulations containing HPMC E 50 as a film-forming polymer it is because of the lower viscosity of HPMC E5 than HPMC E 50. It was observed that, as the concentration of polymer increased, parentage drug release from films was get decreased. All formulated mouth dissolving films (F1-F8) released more than 72% of drug within 15 min. The highest drug release about 98% was observed in formulation F1 and lowest drug release about 73.2% seen in formulation F8 at the end of 15 min. The results are shown in the table 3 and figure 5.

After analysis of all the results it was observed that from all the prepared formulations of mouth dissolving films, formulation F2 showed acceptable results having better physical and mechanical with optimum per cent drug content, lesser disintegration time and maximum *in vitro* drug release of 97.0 %. Therefore formulation F2 containing lower concentration of HPMC E5 as film-forming polymer was considered to be the best formulation and was chosen for further study.

The ex-vivo permeation study indicates permeability of drug through the oral mucosa. Ex-vivo permeation study revealed that 96.5% of a drug gets released within 60 min.from best formulation (F2). The result was given in figure 6.

Table 1: Formulation Of Mouth Dissolving Film Of Paroxetine Hydrochloride By Solvent Casting Method

Formulation Ingredients	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Paroxetine hydrochloride (mg)	10	10	10	10	10	10	10	10
HPMC E5 (mg)	0.15	0.25	0.35	0.45	--	--	--	--
HPMCE 50 (mg)	--	--	--	--	0.15	0.25	0.35	0.45
Citric acid (mg)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium Saccharine (mg)	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
Distilled water (ml)	10	10	10	10	10	10	10	10

Table 2: Physicochemical Properties Of Mouth Dissolving Films Of Paroxetine Hydrochloride

Formulation code	Weight (mg)* (4cm^2 film)	Thickness (mm)*	Folding endurance*	Surface pH*
F1	35.62±2.35	0.12±0.015	282±6.69	6.50± 0.81
F2	47.16±2.06	0.15±0.012	367±7.05	6.56±0.71
F3	60.34±2.12	0.17±0.011	395±8.39	6.65±0.42
F4	72.01±2.24	0.21±0.008	415±10.49	6.81±0.91
F5	36.62±2.00	0.14±0.01	401±12.29	6.76±0.64
F6	46.79±2.82	0.18±0.009	435±12.86	6.72±0.82
F7	61.13±2.97	0.21±0.01	467±12.16	6.83±0.60
F8	71.89±3.03	0.23±0.014	516±12.63	6.75±0.81

*values are expressed as average ±S.D. (n=3)

Table3: Evaluation Parameters Of Mouth Dissolving Film Of Paroxetine Hydrochloride

Formulation code	Disintegration time* (sec)	Tensile strength* (gm/cm^2)	% Elongation*	% Drug content*	% Drug release in 15 minutes*
F1	12.05±1.01	12.20±0.92	12.20±1.12	99.3±2.68	98.0±2.01
F2	18.32±1.42	19.55±1.13	19.55±1.53	99.6±3.03	97.0±2.51
F3	26.04±2.03	23.23±1.44	23.23±1.54	98.8±2.47	89.1±2.87
F4	31.53±1.32	29.50±1.07	29.50±1.67	98.7±2.40	84.3±2.44
F5	21.05±1.22	15.47±0.81	15.47±1.21	99.0±3.23	88.2±2.27
F6	37.14±2.64	21.37±1.15	21.37±1.15	98.8±2.73	80.2±2.54
F7	45.09±2.84	25.22±1.46	25.22±2.16	98.7±2.32	76.1±2.61
F8	58.83±3.03	27.34±1.25	27.34±1.95	98.6±2.56	73.2±2.27

*values are expressed as average ±S.D. (n=3)

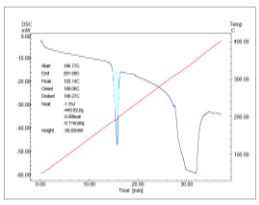

Figure 3: DSC spectra of Paroxetinehydrochloride (Pure drug)

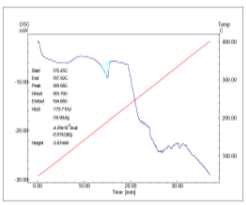

Figure 4: DSC spectra of best formulation (F2) Film

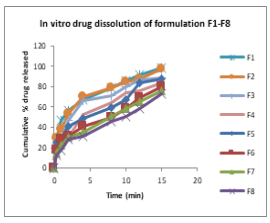

figure 5: In vitro drug dissolution profile of formulations F1 to F8

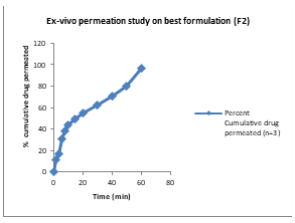

figure 6: Illustration shows ex-vivo permeation study of best formulation F2

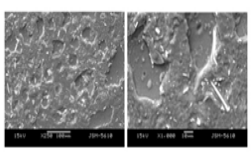

Figure 7: Scanning electron microscopy image of Paroxetine hydrochloride mouth dissolving film.

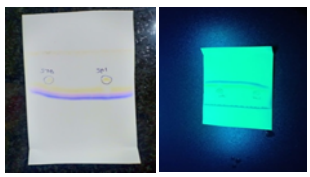

Figure 8: Thin layer chromatography for Paroxetine hydrochloride (standard) and best formulation F2 film (sample)

CONCLUSION

The one of the best (F2) fast dissolving film is successful formulation which provided simple and easily administered dosage form for psychotic patients. This can be attributed to faster dissolution leading to rapid absorption of Paroxetine Hydrochloride from the buccal mucosa and sublingual route which undoubtedly resulted in a decreased presystemic biotransformation and maximized the bioavailabiliy.

Developed Paroxetine hydrochloride film formulations can be promising alternative to conventional oral dosage forms and to achieve earlier onset of action particularly in severe psychotic condition.

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CONFLICT OF INTEREST

There is no conflict of interest.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient, **w/w:**weight by weight, **v/v:** volume by volume, **rpm:** Revolutions per minute, **HPMC:** Hydroxypropyl methylcellulose, **RH:** Relative Humidity,**%:**Percentage, **FT-IR:**Fourier Transform Infrared spectroscopy, **DSC:** Differential Scanning Colorimeter, **UV-vis:** Ultraviolet-visible, **λmax:** Absorption maxima,**r^2:** regression coefficient, **SSRI:** Selective serotonin reuptake inhibitor.

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