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Original Article

PREPARATION AND EVALUATION OF FLOATING EXTENDED RELEASE MATRIX TABLET USING COMBINATION OF POLYMETHACRYLATES AND POLYETHYLENE OXIDE POLYMERS

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ABSTRACT

Objective: The purpose of this study was to prepare non-effervescent floating extended release matrix of Tramadol hydrochloride using polyethylene oxide (PEO) and a combination of cationic and anionic polymethacrylates polymers, Eudragit® EPO (EE) and Eudragit® L100-55 (EL).

Methods: Polymethacrylate polymer mixtures (PPM) in different polymer weight ratios (1:2, 1:1 and 2:1) were prepared by hot melt mixing process. Thermally treated PPM were evaluated by differential scanning calorimetry and fourier transform infrared spectroscopy for possible interpolyelectrolyte complex formation. The formulation variables like effects of polymethacryate ratios and their concentration, polymer types, PEO concentrations and compression force on release characteristics were investigated. The tablets were also evaluated for physicochemical properties,*in vitro* floating ability (floating lag-time and duration) and swelling properties.

Results: The optimized formulation with the combination of PEO and PPM (F4) showed instant floating properties, extended drug release properties for 14h and tablet remained buoyant for >24 h. Significant difference was observed in the effect of pH of dissolution media on drug release from formulations prepared using combination of PEO and PPM. The dissolution data of these matrices were fitted to different dissolution models. Non- Fickian release transport was confirmed as the drug release mechanism from the optimized formulation (F4).

Conclusion: non- effervescent floating tablets were found a feasible approach for the sustained-release preparation of drugs, which have limited absorption sites in the stomach

Keywords: Floating, Extended Release, Polymethacrylates, Polyethylene oxide.

INTRODUCTION

The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time [1]. In recent years, oral dosage forms for gastric retention have received significant interest for their theoretical advantage in permitting control over the time and site of drug release[2]. Several approaches have been reported in the literature for the formulation of gastro retentive drug delivery systems: mucoadhesion [3, 4], flotation[5], sedimentation[6] ,expansion[7] and modified shape systems[8,9]. Both single-unit systems (tablets or capsules) and multiple-unit systems (multiparticulate systems) have been reported in the literature[10,11].

A floating drug delivery system is of particular interest for drugs which: (a) act locally in the stomach;(b) are primarily absorbed in the stomach; (c) are poorly soluble at an alkaline pH; (d) have a narrow window of absorption; and (e) are unstable in the intestinal or colonic environment[12]. Floating systems are either based on an inherently low density or on effervescence. Non-effervescent systems have their inherent low density due to the entrapment of air, as in the formation of low density hollow microballons [13], microspheres [14],incorporation of low density material (sponges) [15,16] or due to swelling [17]. The effervescent systems, on the other hand, have an initially high density, which decreases upon contact with the acidic environment due to CO_2 generation. This is achieved by the incorporation of effervescent components such as sodium bicarbonate or sodium carbonate, and additionally citric or tartaric acid [18]. However, a potential problem with this system is that the tablet could rapidly exit the stomach before becoming buoyant since the device cannot float immediately after administration and its buoyancy will be influenced by fluctuations in the pH of the gastric fluids. In fact, it has been reported that the gastric pH elevates to approximately 5 during a meal [19]. Furthermore, the fasted gastric pH for an achlorhydric subject has been reported to be approximately 7; thus, for such patients, this system would not provide adequate therapy [19].

Polyethylene oxide (PEO) is a high molecular weight, nonionic homopolymer of ethylene oxide with good water solubility. PEOs have been proposed as alternatives to cellulose or other ethylene glycol derivatives in the production of controlled release drug delivery system [20]. PEO, in presence of water or gastric juices, controls the release of the active moiety either by swelling or by swelling/erosion by forming a hydrogel. In this study, high molecular weight PEO (mw = 7×10^6) was used since it is reported that it swells to a greater extent and forms a stronger gel that is less prone to erosion. Further it also has mucoadhesive properties which may assist prolonging the gastric residence time [21]. The drug release rate from hydrophilic matrix can be modified by altering the polymer type, solubility of drug, polymer content, particle size of drug and polymer as well as types and amount of filler used in the formulation [22]. The adjustment of polymer concentration, viscosity grade and addition of different types and levels of excipients to the polymer matrix can modify the kinetics of drug release [23].

Polymethacrylates (Eudragits®) are synthetic cationic or anionic polymers of dimethyl-aminoethylmethacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types of Eudragits® are commercially available and may be obtained as dry powder, granules, aqueous dispersion, or as an organic solution. Eudragit® polymers have been proven to be suitable for a wide variety of pharmaceutical applications; they are primarily used in oral capsule and tablet as film-coating agents for protective purposes and provide delayed and sustained release formulations [24-26]. Eudragit®-EPO (EE), a cationic polymer prepared by copolymerization of butyl methacrylate, 2-dimethylaminoethylmethacrylate, and methyl methacrylate with

molar ratio of 1:2:1. This polymer is used for protective coatings and taste-masking [27]. It is soluble in gastric fluid below pH 5. Eudragit® L100-55 (EL) is an anionic copolymer based on methacrylic acid and ethyl acrylate. It exhibits pH dependent solubility and is soluble at pH values higher than 5.5 [28].

Few papers were devoted to the possibility of involving mixtures of anionic and cationic polymethacrylate polymers in an ionic interaction in order to prepare a new complex. This complex has pH-independent characteristics which can be used in sustained release solid dosage forms [29-31]. Although polymethacrylates are widely used in pharmaceutical delivery systems for sustained drug release, their use in floating sustained release matrix tablets for local drug delivery in the stomach was not routinely addressed in the literature. Bani-Jaber et al., [32]investigated a floating drug delivery system consisting of sodium bicarbonate as an effervescent agent and combination of polymethacrylates (EL and Eudragit® E100) polymers. Fukuda et al., [33]investigated the influence of sodium bicarbonate on the physicochemical properties of controlled release hot melt extruded (HME) tablets containing Eudragit® RSPO and/or EE.

In this current study, non effervescent based floating sustained release matrix tablets were prepared using two oppositely charged polymethacrylates (EL and EE) with combination of hydrophilic polymer as sustained release carrier. Eudragit® polymers were thermally treated and incorporated into tablets to achieve a rapid and pH independent floating systems, preventing premature evacuation through the pyloric sphincter, an inevitable event observed with gas-generating systems [34]. Investigations of the release mechanistics, as well as thermal behavior and molecular interaction of Eudragit® polymer blends were done to elucidate the degree of interaction between Eudragit® polymers which could govern the physical, mechanical and buoyancy properties of the formulated tablets. Tramadol hydrochloride, a highly water soluble drug, is used as a model drug.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride was obtained from matrix laboratories limited (Hyderabad, India) as a gift sample. EE and EL were purchased from EvonikRöhm GmbH (Darmstadt, Germany). Polyethylene oxide (PEO) was purchased from the Dow chemical company (USA). HPMC and Xanthan gum was obtained as gift samples from Matrix laboratories limited (Hyderabad, India). Magnesium stearate was purchased from Avantor (USA)

Methods

Thermal treatment of Eudragit® Polymers

The polymethacrylate polymer mixture (PPM) containing EE and EL in various weight ratios (1:2, 1:2, 2:1) was prepared by mixing them in a stainless steel container at 100°C using a thermostatic heating oil bath (Vision Lab Equipments, India). The resulting homogenous preparations were allowed to cool at room temperature and passed through #30 mesh ASTM sieve and kept in a HDPE bottle until use.

Characterization of PPM

Differential scanning calorimetry

The thermo grams of Tramadol hydrochloride, EE, EL, thermal treated PPM and physical mixture of drug and PPM (1:1) were recorded using a DSC 822e calorimeter (Mettler Toledo, Greifensee, Switzerland). The powders (weight 2–6 mg) were analyzed in analyzed in closed aluminium sample pans and the samples were heated from 30 to 300°C at 10 °C min^{-1}.

Fourier Transform Infrared Spectroscopy.

Infrared spectra of Tramadol hydrochloride, EE, EL, PEO, thermal treated PPM and physical mixture of drug and excipients (1:1) were recorded on Fourier transform infrared (FT-IR) instrument (PerkinElmer,USA) Samples were prepared and compressed with KBr on Minipress (Techno search, India) to form a disk. The compressed disks were scanned over 400 to 4,000 cm−1, and characteristic peaks were recorded and evaluated.

Preparation of Floating Matrix Tablets

Various formulations (Table no.1 and 2) and powder blends were studied based on different proportions of polymers, excipients and their manufacturing processes. Tramadol hydrochloride floating matrix tablets were prepared by direct compression method using hydrophilic polymer (different grades of PEOs or HPMC (K100M) or Xanthan gum) and PPM (different Eudragit® polymer ratio and their concentration). Magnesium stearate was used as lubricant. Drug and polymers, passed through sieve No.30 mesh, were mixed uniformly for 5 minute in a polybag and further mixed with magnesium stearate for 3 minutes. The resultant mixture was then compressed into tablets on a 8- station rotary tablet punching machine (Kambert Machinery Co. Pvt. Ltd, India) using a 10.3 mm standard concave punches with corresponding die to provide a desirable hardness. The tablets were compressed at different hardness for selected formulation. For comparison purpose, tramadol hydrochloride extended release matrix tablets were prepared using Tramaol hydrochloride, PEO 200 mg and magnesium stearate 5 mg using similar manufacturing process as mentioned above. The amount of tramadol hydrochloride in floating tablets was kept constant at 100 mg while the amount of other excipients was varied.

Physical evaluation of the floating matrix tablets

Tablet weight variation is calculated by measuring the weight of ten tablets and the results are expressed as mean values±SD. The hardness and thickness of the matrix tablets were examined for five tablets of each batch using a hardness tester (Dr. Schleuniger, Germany) and a micrometer respectively. Friability of the tablets was measured in a friability tester (Electrolab, India.). The tablets were weighed initially and rotated at 25rpm for 4 min, and the samples were then reweighed. The percentage friability was calculated using the equation:

$$F\% = (W1 - W2)/ W1 \times 100\% \quad \text{.....[1]}$$

where F% represents the percentage weight loss, and W1 and W2 are the initial and final tablets weights, respectively.

The floating lag time and the total floating time buoyancy

The floating lag time and the total floating time were determined by observation of the floating behaviors in the release test using a dissolution tester (Electrolab, India) with the paddle method at a rotation speed of 50 rpm. The dissolution medium was 900 ml of 0.1N HCl (pH 1.2), pH 6.8 phosphate buffer or deionized water at 37 ± 0.5°C. The state of the tablets during buoyancy testing was checked visually for 12h. The time interval between the introduction of the tablet into the release medium and its buoyancy to the surface was taken as floating lag time and the total floating time was observed visually. All buoyancy tests were performed in triplicate.

In-vitro drug release

In-vitro drug release testing from tablets was conducted according to the USP 27 apparatus 2 specifications using a dissolution tester (Electrolab, India). The dissolution testing for tramadol hydrochloride was conducted in 900 ml of 0.1N HCl (pH 1.2) or pH 4.5 acetate buffer or pH 6.8 phosphate buffer. During dissolution testing, the media was maintained at 37±0.5°C. The paddles rotated at a speed of 50 rpm. The tablets were placed into 900 mL of dissolution medium. Aliquots of 8 mL were withdrawn from the dissolution apparatus at different time intervals and filtered through a cellulose acetate membrane (0.45 μm). The drug content was determined spectrophotometrically at a wavelength of 271 nm. At each time of withdrawal, 8 mL of fresh medium was replaced into the dissolution flask. The mean of three determinations was used to calculate the drug release from each of the formulation.

Swelling studies

The swelling of the polymers upon hydration by the test medium was determined by a method similar to the equilibrium weight gain method as reported earlier. The matrix tablets were weighed and placed in tared metallic baskets. These baskets were then immersed in 900 ml of pH 1.2 or pH 6.8 phosphate buffer medium, at 100 rpm and 37± 0.5°C (USP 25 basket method).

At specified time intervals, the baskets containing the matrix tablets were removed, lightly blotted with tissue paper so as to remove excess water and weighed again. They were then placed back in the dissolution vessel as quickly as possible. The percent degree of swelling was calculated as follows [35]:

Percent degree of swelling = [(Ws – Wd) / Wd] X 100 ..... [2]

where Ws is the weight of the swollen matrix at time t and Wd is the weight of the dry matrix. The swelling study was done in triplicate for all samples tested.

Drug release kinetics

To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted in various kinetic models: zero order (Equation 3) as cumulative amount of drug released against time and Higuchi's model (Equation 4) as cumulative percentage of drug released against square root of time.

$$M_t / M_\infty = K_0 t \text{ ..... [3]}$$

Where M_t / M_∞ is the fraction of drug released at any time t; where K_0 is the zero-order rate constant.

$$M_t / M_\infty = K_H t^{1/2} \text{ ..... [4]}$$

where K_H is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time. To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data were also plotted using the Hixson-Crowell cube root law:

$$(Q_0)^{1/3} - (Q_t)^{1/3} = K_{HC} t \text{ ..... [5]}$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in the tablet, and K_{HC} is the rate constant for the Hixson-Crowell rate equation, as the cube root of the percentage of drug remaining in the matrix versus time. The following plots were made: cumulative % drug release versus time (zero order kinetic model); cumulative % drug release versus square root of time (higuchi model) and cube root of drug % remaining in matrix versus time (hixson-crowell cube root law). The model with the highest correlation coefficient was considered to be the best fitting one.

Mechanism of drug release

To study the release kinetics from the floating matrix tablets, the release data were fitted to the well-known exponential equation (power law or Korsmeyer–Peppas equation), which is often used to describe the drug release behavior from polymeric systems [36].

$$M_t / M_\infty = K t^n \text{ ..... (6)}$$

Where M_t / M_∞ is fraction of drug released at time t, k is the rate constant incorporating the structural and geometric characteristics of the matrix tablets and n is the release exponent indicative of the drug release mechanism. To clarify the release exponent for different batches of matrices, the log value of percentage drug released was plotted against log time for each batch according to the equation 7.

$$\log [M_t / M_\infty] = \log k + n \log t \text{ ..... [7]}$$

In case of fickian release (diffusionaly controlled-release), the n has the limiting values of 0.45 for release from cylinders. Case II transport or relaxation controlled delivery; the exponent n is 0.89 for release from cylinders. The non-fickian release or anomalous transport of drug occurred when the n values are between the limiting values of fickian and Case II transport. The non-fickian kinetics corresponds to coupled diffusion/polymer relaxation. Occasionally, values of n > 0.89 for release from cylinders have been observed, which has been regarded as super case II kinetics [36].

Release profiles comparison

The drug release profiles were compared using two model-independent methods, mean dissolution time (MDT) and similarity factor (f2) [37]. MDT was calculated from dissolution data using equation 8, and has been used for comparison.

$$MDT = \frac{\sum_{j=1}^{n} t_j \Delta Q_j}{\sum_{j=1}^{n} \Delta Q_j} \text{ ..... [8]}$$

Where j is the sample number, n the number of time increments considered, t_j is the time at midpoint between tj and t j−1, and ΔQj the additional amount of drug dissolved in the period of time tj and tj−1.

The similarities between two dissolution profiles were assessed by a pair-wise model independent procedure such as similarity factor (f2):

$$f_2 = 50\ Log\left\{\left[1 + \frac{1}{n\sum_{t=1}^{n=t}(R_t - T_t)^2}\right]^{-0.5} \times 100\right\} \text{ ..... [9]}$$

Where n is the number of pull points, R_t is the reference profile at time point t, and T_t is the test profile at the same time point; the value of f2 should be between 50 and 100. An f2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between release profiles increases.

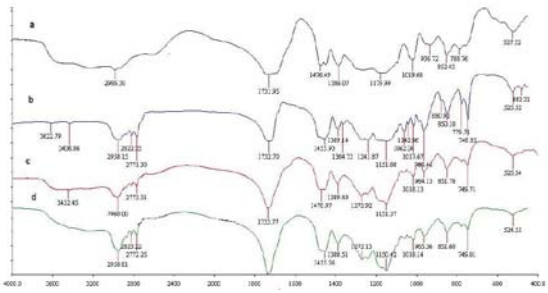

Fig. 1: FT IR spectrum of EL (a), EE (b), physical mixture (c) and heat treated polymer mixture (PPM) (d).

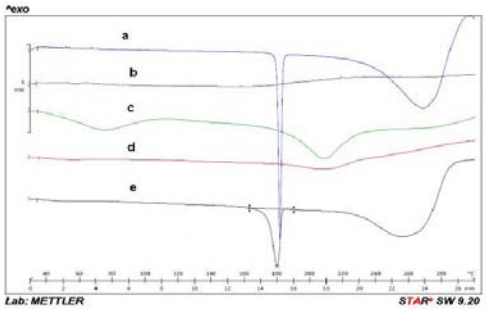

Fig. 2: DSC spectrum of tramadol (a), EE (b), EL (c), PPM (d) and physical mixture of tramadol and PPM (e)

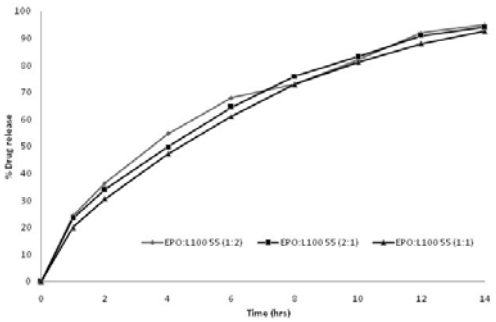

Fig. 3: Comparative dissolution profiles showing the effect of different Eudragit® ratio on release of tramadol from floating matrix tablets. Each data point represents the average of 3 tablets from three batches with SD within ±3.0.

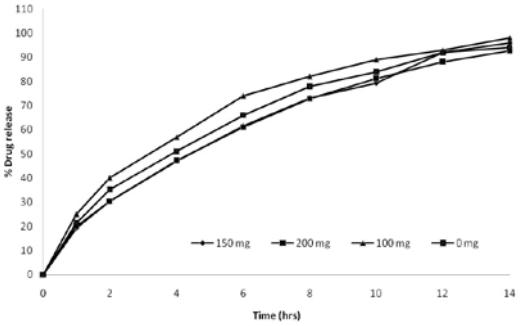

Fig. 4: Comparative dissolution profiles showing the effect of different polymer concentration on release of tramadol from floating matrix tablets. Each data point represents the average of 3 tablets from four batches with SD within ±3.0.

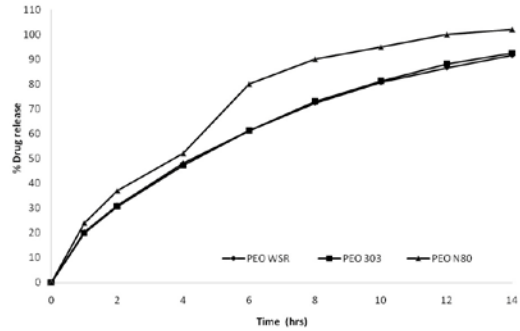

Fig. 5: Comparative dissolution profiles showing the effect of different PEO grades on release of tramadol from floating matrix tablets PEO grade. Each data point represents the average of 3 tablets from three batches with SD within ±3.0.

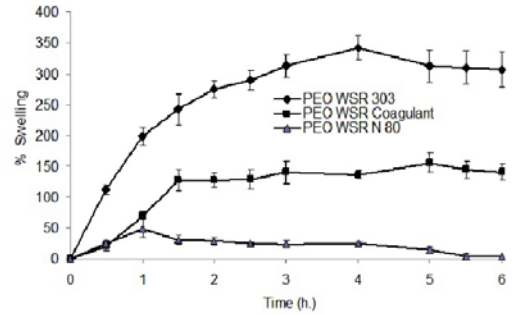

Fig. 6: Swelling index of matrix tablet prepared with different PEO polymer grades (n=3).

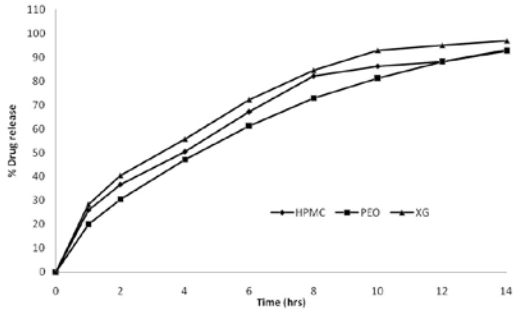

Fig. 7: Comparative dissolution profile of tramadol floating matrix tablet prepared with different hydrophilic polymer types. Each data point represents the average of 3 tablets from three batches with SD within ±3.0.

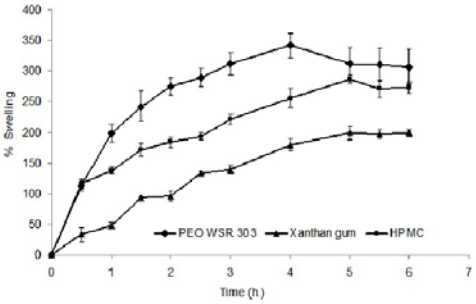

Fig. 8: Swelling index of matrix tablet prepared with different hydrophilic polymer grades (n=3).

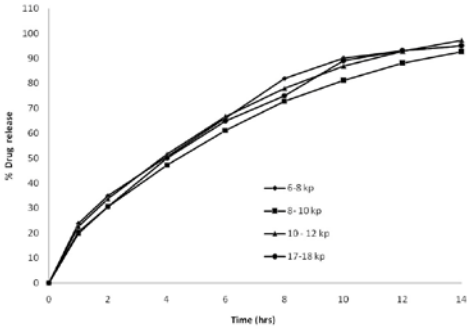

Fig. 9: Comparative dissolution profile studies of tramadol floating matrix tablet prepared with different tablet hardness. Each data point represents the average of 3 tablets with SD within ±3.0.

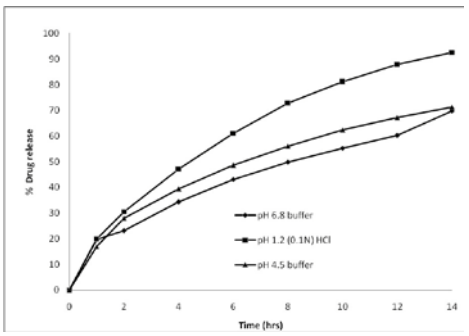

Fig. 10: Comparative dissolution profiles showing the effect of dissolution medium type on release of tramadol from floating matrix tablets. Each data point represents the average of 3 tablets with SD within ±3.0.

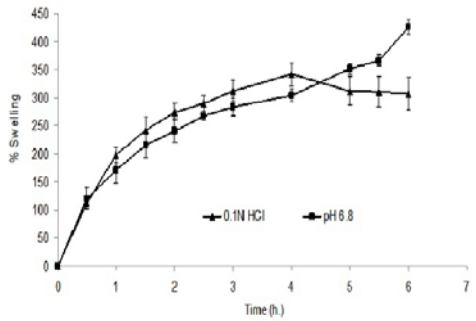

Fig. 11: Swelling index of matrix tablet in different dissolution medium (0.1N HCl and pH 6.8 buffer) (n=3).

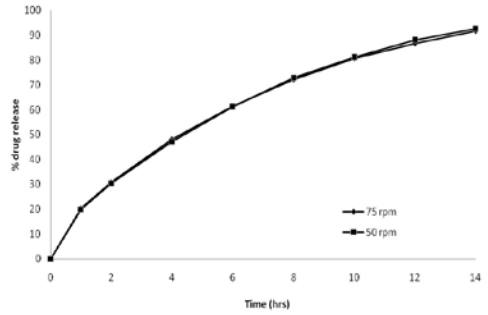

Fig. 12: Comparative dissolution profiles showing the effect of agitation speed on release of Tramadol from floating matrix tablets. Each data point represents the average of 3 tablets with SD within ±3.0.

RESULTS AND DISCUSSION

Characterization of thermal treated PPM

FT-IR has been used for studying chemical interactions at a molecular level in polymer-polymer blends in the inter poly electrolyte complex field. This analysis was focused on the changes in bands associated with the polymers amino and carboxylate groups. If the two polymers ionically interacted in the complex, then the functional groups in the IR spectra would show the emergence of additional bands, alterations in the wave number position or broadening, compared with pure polymer spectra [38]. The FT-IR spectra of EL, EE powder, physical mixture of EE/ EL and treated PPM in a 1:1 weight ratio, respectively are shown in figure 1a-d. Since EE and EL belong to the same class/ derivatives of methacrylic acid copolymers - the FTIR spectra would exhibit many common features.

EE showed a characteristic band at 1,732 cm^{-1} which corresponds to absorption of ester groups in addition to two more absorption bands at 2,771 and 2,822 cm−1 which corresponds to the optical absorption due to non-ionized dimethyl amino groups [31]. On the other hand, the spectrum of EL showed similar but broader absorption band for the nonionized carboxylic acid groups at 1,732 cm−1 than that found in EE due to the intra- and intermolecular hydrogen bonding between the carboxylic acid groups [39].

Moreover, EL also showed a wide absorption range of the associated hydroxyl groups between 2,500 and 3,500 cm^{-1} but this was not clear from the figure; rather, several minor peaks have been observed in this range. As can be seen from the figure 1C, the FT-IR spectrum of the physical mixture EE and EL seemed to be a superposition of the spectra of the two polymers and no new peaks were observed suggesting that only minimum, if any, interaction could be found between EE and EL in their powdered base forms.

However, a possible ionic interaction between EE and EL would be expected to have some impact on the shape of the FT-IR spectrum. Figure 1d showed the FT-IR spectrum for treated PPM prepared by hot mixing of EE and EL.

Table 1: Composition of tramadol floating matrix tablets

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Tramadol Hydrochloride	100	100	100	100	100	100	100
2	Polymethacrylate mixture (1:1)	--	100	150	200	--	--	200
3	Polymethacrylate mixture (1:2)	--	--		--	200	--	--
4	Polymethacrylate mixture (2:1)	--	--	--	--	--	200	--
5	PEO WSR 303	200	200	200	200	200	200	100
6	Magnesium stearate	5	5	5	5	5	5	5
	Total (mg)	305	405	455	505	505	505	405

Table 2: Composition of tramadol floating matrix tablets

S. No.	Ingredients	F8	F9	F10	F11
1	Tramadol Hydrochloride	100	100	100	100
2	Polymethacrylate mixture (1:1)	200	200	200	200
3	PEO WSR coagulant	200	--	--	--
4	PEO WSR N80	--	200	--	--
5	HPMC	--	--	200	--
6	Xanthan gum	--	--	--	200
7	Magnesium stearate	5	5	5	5
	Total (mg)	505	505	505	505

Table 3: Tablet physical parameters and floating properties

Formulation code	Ave weight (mg)	Thickness (mm)	Hardness (kp)	Floating lag time	Total floating time (h)
F1	305 ± 1.4	4.49 ± 0.02	6-8	NF	NA
F2	405 ± 1.6	5.76 ± 0.03	6-8	NF	NA
F3	455 ± 1.4	6.74 ± 0.03	7-9	2-3 s	>24
F4	505 ± 1.7	7.23 ± 0.04	8-10	2-3 s	>24
F5	505 ± 1.3	7.34 ± 0.03	8-10	2-3 s	>24
F6	405 ± 1.2	7.15 ± 0.05	8-10	2-3 s	>24
F7	505 ± 1.5	5.98 ± 0.06	8-10	2-3 s	>24
F8	505 ± 1.1	7.22 ± 0.03	8-10	2-3 s	>24
F9	505 ± 1.4	7.13 ± 0.03	8-10	2-3 s	>24
F10	505 ± 1.8	7.08 ± 0.03	8-10	NF	NA
F11	505 ± 1.6	6.75 ± 0.02	8-10	NF	NA

NF: Not floating after1h

Table 4: MDT and T 50 % of tramadol matrix tablets

Formulation Code	MDT	T_{50}%
F1	4.3	3.80
F2	4.1	3.27
F3	5.0	4.38
F4	4.7	4.39
F5	4.4	3.49
F6	4.5	3.94
F7	3.7	2.92
F8	4.7	4.33
F9	4.0	3.24
F10	4.1	3.63
F11	3.8	3.06

Table 5: Release kinetic parameters of the selected formulation

Formulation Code	Zero order		Higuchi's model		Hixson-Crowell model		Korsmeyer-Peppas model		
	r	K_0	r	K_H	R	K_{HC}	r	K_p^{-n}	n
F4	0.936	6.293	0.996	27.48	0.997	0.187	0.999	19.815	0.626

Formation of IPC between the anionic polymer (EL) and the cationic polymer (EE) has been reported by various research groups. The FT-IR spectrum of treated PPM (figure 1D) does not demonstrated any such formation of IPC similar to those published in the literature. Several authors reported that when IPC is formed between EE and EL, the FT-IR spectrum showed several new peaks at 1,751 and 1,542 cm^{-1} that might be assigned to the ionized carboxylate groups and hydrogen bonded carbonyl groups accompanied by the decrease in intensity of band corresponding to the nonionized carboxylic acid group [30]. Further, a decrease in the intensity of the non-ionized dimethylamino group in addition to the formation of weak bands in the range of 2,770–2,830 cm−1 might be due to the interaction of protonated dimethylamino group from EL with carboxylate group from EE. Based on the above facts, it is confirmed that no such interactions peaks were observed in FT-IR spectrum of treated polymethacrylate powder mixtures.

Differential scanning calorimetry

DSC thermogram of pure drug, EE, EL, PPM and physical mixture of drug and PPM are shown in figure 2a-e. EL showed a broad endothermic band ranging between 50 and 100°C, due to the polymer dehydration, followed by a second endothermic effect at higher temperature, attributable to the melting of its crystalline portion [40]. Glass transition temperature (Tg) of EE was observed around 50°C and no major thermal events in the thermogram indicated the amorphous nature of the material. For treated PPM, a broad endothermic peaks observed around 210°C indicated the reduced crystalinity of EL. Tramadol hydrochloride showed two endothermic peaks: one sharp peak at 180°C corresponding to the melting point of the drug and one broad endothermic peak around 270 °C corresponding to the degradation of drug. There was no significant interaction between tramadol hydrochloride and treated PPM as the thermograms of the drug and treated mixture showed melting endotherms of similar temperatures.

Characterization of matrix tablets

The results indicated that all the tablets prepared in this study meet the USP 29 requirements for weight variation tolerance. The thickness and hardness variation of the individual tablet batches was within ± 3 SD (Table 3). The friability was found to be less than 1%w/w for all the formulations evaluated. These results indicated that the direct compression method is an acceptable method for preparing good quality floating matrix tablets of tramadol.

***In Vitro* buoyancy**

During preliminary study, matrix tablet prepared with only EE found to disintegrate rapidly in the pH 1.2 medium when tested for buoyancy. Matrix tablet prepared using physical mixture of both Eudragit® polymers (EE and EL) were found to float in the medium. However, the tablets were found to disintegrate and lost its matrix integrity after 3-4 hours of floating. Obeidat et al.[30-31] also reported the similar observations. However, matrix tablets prepared using treated PPM showed instant floating behavior and the matrix tablet integrity was found good even after 12 h of testing. Based on these observations, we have selected the treated PPM as floating aid for the preparation of floating matrix tablets. Matrix tablet prepared using only PEO as polymer showed no floatation in 0.1N HCl. Floating lag time and total floating time for the various formulations prepared are shown in table 3. The floating behavior of the formulations was found to be dependent on the concentration of treated PPM as well as the other polymer types used in the formulations. The change in ratio of Eudragit® mixture and the PEO grade did not have any negative impact of the floatability of the matrix tablets prepared. Immediate floating of the tablet was observed in pH 1.2, pH 6.8 phosphate buffer as well as in water. This type of system will be considered advantageous where floating of the matrix tablet will occur irrespective of the gastric pH of the stomach.

Drug-release studies

Effect of Eudragit® ratio and their concentration

EE and EL are quite different in solubility. Therefore, the EE/EL ratio in the tablet might considerably affect the hydration property and drug diffusion coefficient in the matrix. In order to evaluate this effect and to study the effect of EE/EL ratio on floating lag time, three formulations containing different weight ratios (1:2(F5), 1:1(F4) and 2:1(F6)) of EE and EL were prepared. The concentration of treated PPM was set at a fixed quantity of 200 mg/tablet. The drug release profiles from these formulations are shown in figure 3. The release of the drug from formulation with different EE/EL ratios was found to be similar based on similarity factor. The f2 values determined by comparing drug release profiles of 1:1 ratio with 1:2 and 2:1 were found to be greater than 63.8 and 73.9 respectively. The MDT and t_{50} % values were found to be comparatively similar for all the hardness range evaluated (Table 4). Floating lag time and total floating time were found to be similar and not affected by the EE/EL polymer ratios. Different concentration of treated PPM can also affect the floating ability, when the concentration of polymer mixture was under 100 mg/tablet, the floating lag time was significantly delayed (>1 h), the tablets were not light enough to float within 3 min. The floating lag time was found to be under 10s and the total floating time was found to be more than 24h but when the PPM concentration was more than 150 mg/tablet and compressed at the hardness levels of less than 12kp. The drug release profiles from formulations containing different concentration of polymethacrylates are shown in figure 4 and found to be comparable. The f2 factor values were found to be more than 50 when the formulation without polymethacrytalte mixture was compared to formulations containing different concentrations of polymethacrylates mixtures.

Effect of PEO grade and concentration

PEO is a hydrocolloid gelling agent. Upon contact with gastric fluid, PEO takes up water and when water penetrates the matrix, the polymer chains become hydrated and these eventually disentangle from the matrix. At high polymer concentrations, the linear polymer chains entangle to form what may be considered 'virtual cross-linking' which eventually erodes, resulting in drug liberation. However, the rate of polymer erosion is dependent on the viscosity of the PEO grade that is used in the formulation. PEO WSR 303 has a high molecular weight and is of high viscosity grade, it is relatively resistant to polymer erosion compared to the low molecular weight and low viscosity grades [41]. The effect of viscosity of PEO on the drug release was evaluated and shown in figure. 5. The concentration of each type of PEO (Polyox WSR N80 (F9), Polyox WSR coagulant (F8) and Polyox WSR 303(F4)) was set at a fixed quantity of 200 mg/tablet. As the viscosity of PEO was increased from WSR N80 to WSR coagulant, the release rate was decreased. Drug release at 12 h in these formulations was 100% and 87% respectively. The drug release was fastest in PEO WSR N80 formulation with a K value of 23.55% $h^{-0.641}$ and t_{50}% value of 3.24 h. The drug release was slowest in PEO WSR 303 formulation with a K value of 20.28% $h^{-0.616}$ and t_{50}% value of 4.33 h. This observation was agreed with other reports [41]. The release rate was faster with lower viscosity grades of PEO, probably owing to less polymer entanglement and less gel strength. As it clear from the figure 5, there is no difference in the drug release profile between formulations containing Polyox WSR coagulant and Polyox WSR 303 grades (f2 = 97).

The swelling behavior of various polymer blends was analyzed to compare their water uptake capacity. The rate of swelling for matrix tablets that contained different PEO grades is shown in figure 6. Swelling of the matrix, which is indicated by the transition of the polymer from the glassy to the rubbery state, is an important parameter in the determination of the release characteristics of the matrix system [42]. The correlation of polymer swelling to drug release can help explain why different polymer blends gave different mechanisms of release. Fig.6 showed that matrices which contained high molecular weight PEO showed significant swelling over time ($P<0.05$). The highest degree of hydration was achieved by the Polyox WSR 303 tablet. There was about 300% weight gain at the end of 6 h due to swelling in these matrices. On the other hand, formulation containing low molecular weight Polyox WSR coagulant was hydrated to a much lower extent compared to Polyox WSR 303 matrix tablets. These matrices could hydrate only up to 5 h after which there was no further increase in the tablet weight due to water uptake. For the Polyox WSR N80 matrix, low swelling and erosion of the matrix tablet was observed after 5 h.

Effect of polymer type

The effect of different hydrophilic polymers (Xanthan gum (F11), HPMC (K100M) (F10) and PEO (Polyox WSR 303) (F4) on drug release property was studied and shown in figure 7. The effect of polymer types on tablet buoyancy was also evaluated. The MDT and t_{50} % values of Xanthan gum, HPMC and PEO formulations were found to be 3.8, 4.1, 4.7 h and 3.06, 3.63, 4.39h, respectively. The drug release from the formulation containing xanthan gum (F11) was found to be slightly faster than the formulations containing other two polymers. The f2 factor value was observed to be 49.67 between Xanthan gum and PEO formulations, indicating the difference between the release profiles, whereas the f2 factor values were found to be 77.83 between HPMC and PEO formulations, indicating no difference between the release profiles of HPMC and PEO formulations.

The nature of the polymer plays an important role in this swelling process of the matrix tablets. Swelling studies were carried out, in order to investigate whether the extent of swelling varied for the different formulations. The results obtained from these swelling studies are represented in figure 8. From analysis of this data, it was possible to conclude that for the xanthan gum containing matrix tablets, the amount of aqueous uptake absorbed (and consequently the degree of swelling) was lower than for formulations containing HPMC or PEO. The faster drug release from the xanthan gum based formulations can be attributed to the low viscosity and low swelling of the polymer. The floating lag time was found to be higher (> 1h) for HPMC and Xanthan gum based formulations compared to the PEO based formulations (<10 seconds) compressed at the same hardness level (8-10 kp).

Effect of Hardness on Drug Release

The effect of tablet hardness on the drug release was studied by preparing tablets using same type of polymer and same polymer proportion but with different hardness levels, 6–8, 8–10, 10-12 and 17–18 kp. As shown in figure 9, the release of the drug from formulations compressed at different hardness levels were found to be similar based on similarity factor. The f2 values determined by comparing drug release profiles of 8-10 kp with 6-8 kp, 10-12 kp and 17-18 kp was found to be 60, 66.5 and 70.1 respectively. The tablets compressed at hardness levels beyond 12 kp was found to be non floating and indicated that the tablet density may be higher than 1.0mg/mm^3. Tablets compacted at a hardness level of less than 12 kp, keep more entrapped air, decreasing the agglomerate density and allowing the tablets floating. On the other hand, tablets compacted at higher pressure are less porous and display a density not allowing the matrices floatation.

Effect of dissolution media on drug release

The investigation of the effect of various dissolution media on the release profile of drug from the dosage form is important because the dosage form will encounter environments of differing pH during its transit in the gastrointestinal tract. The effect of dissolution media (pH 1.2, 4.5 and 6.8) on the drug release from selected formulation (F4) are shown in Fig. 10. The f2 values determined by comparing drug release profiles in pH 1.2 with pH 6.8, pH 4.5 with pH 6.8 and pH 1.2 with pH 4.5 were found to be 38.4, 62.9 and 46.0 respectively for the selected formulation (F4); The drug release was fastest in pH 1.2 with a K value of 19.815% $h^{-0.626}$ and t_{50}% value of 4.39 h. The drug release was slowest in pH 4.5 and pH 6.8 buffer with a K value of 17.906% $h^{-0.553}$ and 18.24 % $h^{-0.489}$, t50% value of 6.4 h and 8.4 h respectively. The values of n for the selected formulation (F4) in pH 1.2, 4.5 and 6.8 were found to be 0.626, 0.553 and 0.475 respectively, indicating that the mechanism of drug release from the formulations across the pH range of 1.2 - 6.8 was found to be similar and follows non-ficikian or anomalous diffusion mechanism

The observed difference in release rate in different dissolution medium could be attributed to differences in polymer characteristics in different media than due to the drug. This is because tramadol hydrochloride has pH independent solubility. The difference in dissolution profiles of selected formulation (F4) was due to the difference in the ionization of polymethacrylates in different dissolution media because of which there was a difference in swelling, gel strength and diffusional path length of the matrix. The % swelling at 6h in pH 1.2 and pH 6.8 buffer medium was found to be 307 % and 427 % respectively, indicated higher degree of swelling in the later dissolution medium and slower release rate (figure 11). As the pH of media increases, the ionization of carboxylic groups (present in the Eudragits® polymer) increases and could leads to the formation of in-situ interpolyelectrolyte complexes between the oppositely charged Eudragit® polymers and because of this swelling and diffusional path length of the matrix increases. Formation of interpolyelectrolyte complex between the cationic polymer (EE) and anionic polymer (EL) has been reported by various research groups. Bani-Jaber et al. [32] reported that when sodium bicarbonate, an alkaline excipients, was added to the Eudragit® mixed matrix system, it provided increased in micro-environmental pH around EL particles leading to the ionization of EL and consequently EE and EL complexation. Based on this, slower drug release rate in pH 4.5 and pH 6.8 buffer medium compared to drug release rate in pH 1.2, could be attributed to the formation of interpolyelectrolyte complex formation in these dissolution conditions. Ionic interaction between two oppositely charged polymers and subsequent in-situ interpolyelectrolyte formation was reported when the binary mixtures of polyvinylacetate phthalate and EE were exposed to pH 5.5 acetate or pH 6.8 phosphate buffer [43].

Effect of Agitation Speed on Drug Release

It is known that the drug release rate from the delivery system shall be influenced by the factors that influence dissolution such as the thickness of the diffusion boundary layer if it is controlled by the dissolution of drug. The aqueous diffusion boundary layer around the matrix offers significant resistance to the dissolution of poorly soluble drug. The thickness of the aqueous diffusion boundary layer is affected by the rate of agitation speeds in the dissolution medium: the higher the agitation rate, the thinner the aqueous diffusion boundary layer [44]. If the release of tramadol is solely controlled by its dissolution in the release medium, then increasing the agitation rate should accelerate the release of tramadol. The effect of agitation speed on the in vitro release profiles of drug from selected formulation (F4) in 900 ml of pH 1.2 (0.1N HCl) is shown in figure 12. No significant difference was observed in the release rate with increase in agitation speed from 50 rpm to 75 rpm as indicated by the f2 value (f2>97). MDT and t_{50}% values are found to be similar for both the agitation speed (MDT of 4.7h and t_{50} % of 4.39h for 50 rpm and MDT of 4.7h and t_{50}% of 4.33 h for 75 rpm).

Release Kinetics

To analyze the mechanism of drug release from the matrix-tablets, the dissolution data were fitted to various kinetic models, the release kinetic parameters and the fitting ability (correlation coefficient, r) for the selected formulation (F4) is listed in Table 5. The n values of 0.626 indicated an anomalous diffusion mechanism for this formulation. Also, both Higuchi model (Fickian) and Hixcon – crowell model kinetics were fitted similarly well.

CONCLUSION

This study examined the preparation of a floating matrix tablet containing Tramadol HCl using the synthetic polymer PEO and thermally treated polymethacrylate mixtures as retarding polymers. The combination of PEO and polymethacrylate mixtures was found to achieve optimum *in vitro* release and floatability. The prepared tablets could float within 1 min and maintain for more than 24 h. The drug release at 12 h was more than 85%. The uniformity of weight, hardness, friability, drug content were all lying within the limit. The matrix integrity, swelling, *in vitro* drug release studies, and kinetics of release data were shown to depend on the type and composition of the polymer blends with polymethacrylate mixtures. The buoyancy of the tablet achieved was found to be pH independent. Therefore, the non- effervescent floating tablets are a feasible approach for the sustained-release preparation of drugs, which have limited absorption sites in the stomach.

CONFLICT OF INTERESTS

Declared None

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