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Research Article

Development and evaluation of biodegradable controlled release microspheres of venlafaxine

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In this study we developed and evaluated stable, biodegradable microspheres for controlled release of venlafaxine. For this purpose, polycaprolactone, a hydrophobic polymer was used in different ratios. Following are the drug to polymer ratios P1 (1:1), P2 (1:1.5), P3 (1:2), P4 (1:2.5) and P5 (1:3); employed to develop controlled release microspheres. Drug loading efficiency increased with increasing quantity of polycaprolactone. The mechanism of venlafaxine release was studied by applying First order, Zero order, Higuchi's, Hixon-Crowell and korsmeyer-Peppas models to dissolution data. Higuchi model was found the best fit model followed by First order release. The mechanism of release was non-Fickian diffusion. All formulations showed an initial burst of 69.53%, 62.37%, 55.45%, 53.76% and 49.32% from P1, P2, P3, P4 and P5 formulations, respectively at the end of 1st h dissolution. P5 was the superior formulation in terms of reduced initial burst and after which sustained release occurred up to 8 hours. The developed microspheres were characterized by Fourier transform infra-red spectroscopy, scanning electron spectroscopy, differential scanning calorimetry and thermogravimetric analysis.

Keywords: Venlafaxine, Biodegradable, Microspheres, Polycaprolactone, Release kinetics.

1. INTRODUCTION

Over the past 50 years, polymeric microparticles have attracted a great focus in biomedical field particularly in drug delivery. Polycaprolactone (PCL) is Food & Drug Administration (FDA) approved slowly degrading polymer. It degrades through ester linkages. Many drugs have been encapsulated into PCL microparticles. PCL produce lesser acidic environment on degradation compared to poly lactic acid (Sinha *et al*., 2004; Bock *et al*., 2011).

Over the past few decades, biodegradable microparticles have attracted a great attention in development of controlled release formulations (Park *et al*., 2005; Jeong *et al*., 1997; Hejazi *et al*., 2003). Biodegradable polymers degrade to compatible products either through chemical or enzymatic hydrolysis. Biodegradable microspheres have shown a promising ability for controlled release of a large variety of drugs regardless of low or high water solubility. The rate of release of drug through biodegradable microspheres can be controlled by biodegradation kinetics of polymer, physiochemical attributes of polymers and drugs, thermodynamic compatibility and shape and size of device (Jain, 2000; Berkland *et al*., 2002; Sinha *et al*., 2003; Mi *et al*., 2002; Abraham *et al*., 2003; Liu *et al*., 2004; Chen *et al*., 2001; Tunon *et al*., 2003).

Polycaprolactone is a white to off-white, thermoplastic, semi-crystalline, linear polyester. Commercially, PCL is produced by ring opening polymerization of lactone. It is a biodegradable polymer derived from petroleum products. PCL can be degraded and mineralized by many microorganisms. Melting point of PCL is approximately 62°C and sealing temperature is 22°C. PCL is finely soluble in ethyl acetate, chloroform, acetone, dichloro methane, toluene, dimethyl sulfoxide and dimethyl formamide. PCL is insoluble in n-hexane, isopropyl alcohol and methanol (Chitra *et al*., 2010). Synthetic polymers are versatile polymers that have a great number of properties to be used in biomedical applications. They are being applied in controlled drug delivery, nano particulate formation, macromolecular drug carriers, stabilizing agents, implants and diagnostic agents (Moghimi *et al*., 2001).

Biodegradable polymers are preferred choice for development of controlled drug delivery devices. Biodegradable polymers offer certain advantages like improving bioavailability, reducing systemic side effects, protecting drug molecules from biochemical degradation, enhance drug targeting and specificity. PCL possess low immunogenicity and toxicity. It exhibits high compatibility. Physiochemical and mechanical properties of PCL can be tailored to develop suitable drug carriers. On degradation, PCL does not produce acidic components. PCL is slowly degraded compared to that of poly lactic acid and poly glycolic acid which make it a suitable biomaterial (Enayati *et al*., 2010). PCL has well established biocompatibility profile. It is being used in/as controlled drug delivery, dermal filler, wound dressing, oral and maxillofacial surgery (Sinha *et al*., 2004). PCL is a non-toxic bioresorbable polymer that degrades in a safe way (deMelo *et al*., 2012). Slow biodegradation of PCL produce a sustained release of entrapped drug for a prolonged period of time (Vilar *et al*., 2012). PCL is a semi crystalline synthetic polyester used extensively in medical and drug delivery devices. It contains aliphatic ester linkages susceptible to both hydrolytic and enzymatic degradation (Alzet *et al*., 2008). de la Ossa and coworkers prepared PCL microspheres using O/W solvent evaporation method. The loaded drug, cannabinoids was slowly released in-vitro within ten days (de la Ossa *et al*., 2012). Microencapsulation of water soluble drugs with conventional O/W solvent evaporation method causes rapid partitioning of drug from organic solvent to aqueous phase with no or little amount of drug loading. Smart modification of conventional method has been reported to overcome this problem. O/O type microspheres can be prepared by dissolving polymer and drug in organic phase and then dispersing it to immiscible oil phase. The elimination of aqueous phase suitably reduces the partitioning of water soluble drug into continuous phase provided that drug is immiscible with oil. Sturesson *et al*., prepared O/O based microspheres of timolol maleate. Poly lactic-co-glycolic acid (PLGA) and drug were dissolved in acetonitrile; sesame oil was the immiscible continuous phase and span 80 was used as emulsion stabilizer. Microspheres were separated by filtration and washing with n-hexane. PLGA microspheres showed an initial burst release, then a slow phase followed by secondary burst (O'Donnell *et al*., 1997; Bodmeier *et al*., 1987; Sturesson *et al*., 1993). In this work, we make an effort to prepare controlled release microspheres of venlafaxine using different ratios of PCL. Venlafaxine is a highly water soluble drug having water solubility of 572 mg/ml (Ali *et al*., 2014). Simple O/O solvent evaporation method was applied to develop free flowing microparticles. The prepared microparticles were evaluated for percent recovery, drug entrapment efficiency, morphology, micromeritic properties, dissolution, compatibility and thermal stability.

2. MATERIAL AND METHODS

Polycaprolactone (Mol. Wt. 80000) and dichloro methane were purchased from Fluke, Buch Switzerland. Corn oil, n-heptane, potassium dihydrogen phosphate, ethanol, span 85 and hydrochloric acid were purchased from Biosciences, England. Corn oil was obtained from Cheil Jedang Corp., Korea.

2.1 Preparation of Microspheres

Venlafaxine microspheres were prepared using solvent evaporation method. The polymer was dissolved in various ratios in dichloro methane by stirring at 400 rpm for 0.5 h. The drug was added to polymer solution and dispersed for five minutes on ultrasonic bath. Corn oil was taken in 250 mL beaker along with Span 85. The dispersion containing the drug and polymer was slowly added drop by drop to 250 mL beaker containing 120 mL of corn oil. The corn oil was stirred continuously at 600 rpm with magnetic stirrer for 5 h till complete evaporation of organic solvent. The microspheres were collected and washed on filter paper under vacuum filtration. The filtered microspheres were rinsed with small quantity of distilled water and washed with n-heptane 4-5 times in order to remove the adhered oil. The prepared microspheres were dried at 40°C in hot air oven (Memmert, Germany). The dried microspheres were stored in air-tight glass jars.

2.2 Percent Recovery

Percent product recovery of PCL microspheres was calculated using following mathematical relation:

$$\text{Product recovery} = \frac{\text{Mass of microspheres}}{\text{Theoretical mass of polymer} + \text{drug}} \times 100$$

2.3 Encapsulation Efficiency

Encapsulation efficiency of PCL microspheres was measured by dissolving accurately measured weight (20 mg) of P1, P2, P3, P4 and P5 microspheres in 20 mL dichloromethane: distilled water (50:%50) and 3 mL ethanol was added to precipitate PCL. Dichloromethane dissolves the PCL layer. The solution was filtered through Millipore and diluted suitably with distilled water. The filtrate was stirred

for one h at 40°C to remove the organic solvent. After evaporation of organic solvent the absorbance of venlafaxine was measured at 226 nm using a UV-VIS spectrophotometer (UV-1100, Schimadzu). Encapsulation efficiency of PCL microspheres was calculated as follows (Sivabalan et al., 2012):

$$\text{Encapsulation efficiency (\%)} = \frac{\text{Calculated venlafaxine concentration}}{\text{Theoretical venlafaxine concentration}} \times 100$$

2.4 Tapped Density

Packing properties of microparticles into capsules can be measured using tapped density. Tapped density also influence flow and mixing properties of microspheres in preparation of tablets. The tapped density of microspheres was measured by using a 10 mL measuring cylinder and total number of tapings was fixed to 100. 100 tapings are sufficient to achieve plateau condition. Following formula was used to calculate tapped density (Shariff et al., 2007).

$$\text{Tapped density} = \frac{\text{Mass of microparticles}}{\text{Volume of microparticles after 100 tapings}}$$

2.5 Angle of Repose

To measure the angle of repose, microparticles were passed through a funnel on a flat surface. The radius (r) and height (h) of microparticle heap achieved after passing through funnel on flat surface was also measured. Following relation was applied to calculate angle of repose:

$$\text{Tan } \theta A = \frac{h}{r}$$

2.6 Hausner's Ratio

Flowability microparticles can be assessed by calculating Hausner's ratio. It can be calculated by following relation:

$$\text{Hausner's ratio} = \frac{\text{Volume of microparticle before tapping}}{\text{Volume after tapping}}$$

A value of Hausner's ratio less than 1.2 indicates good flow.

2.7 Carr's Index

It is also called compressibility index. Carr's index is an indirect measure of size, shape, cohesiveness and bulk density of microparticles. Following formula was used to measure Carr's index:

$$\text{Carr's index} = \frac{\text{Initial volume} - \text{Final volume}}{\text{Initial volume}} \times 100$$

2.8 FTIR

FTIR analysis was carried out to study the interactions between PCL and venlafaxine hydrochloride. The spectra were obtained for pure venlafaxine, PCL and drug-loaded microspheres. Midac USA 2000 FTIR instrument was used to record spectra. Samples were prepared using KBr discs. The spectra were recorded at a scanning range of 500-4000 cm-1 at resolution of 2 cm-1.

2.9 Thermal Analysis

Thermogravimetric and differential scanning calorimetry of pure venlafaxine, PCL and venlafaxine-loaded microspheres were carried out simultaneously using Q600 simultaneous DSC/TGA Analyzer, USA. Microspheres were crushed and a small amount (4-5 mg) was placed in aluminium pans and sealed for test. The sealed sampled were heated at a rate of 20°C per minute. All experiments were performed under nitrogen atmosphere at a rate of 25 mL per minute over the temperature range of 25°C to 400°C. The instrument was calibrated using Indium.

2.10 In-vitro Release Properties

Measured quantity of microparticles was placed in dialysis bag and tied to paddle of USP dissolution apparatus II. Buffer of pH 7.4 was used as release media. The volume of release media was 900 mL and paddle speed was 50rpm. Temperature of release media was maintained at 37±1°C throughout the study. An aliquot of 2mL was collected at various time intervals and replaced with fresh equal amount of buffer. The aliquot was suitably diluted with distilled water and analyzed at 226 nm spectrophotometrically. The amount of drug released at each time interval was measured by using standard calibration curve. The cumulative release was calculated by following relation:

$$\text{Cumulative release} = \frac{F_t}{F_\infty} \times 100$$

Where, Ft and $F\infty$ represent amount of drug released at time t and total amount of drug released from microspheres, respectively.

2.11 Mathematical Modeling

Drug release from various drug delivery devices is assumed to follow different mechanism and patterns. Mathematical modeling of release data is commonly performed to assess the mechanism of drug release from different carriers. Zero order release equation describes that drug release is at constant rate and is

independent of its concentration (Najib et al., 1985).

First order equation explains systems where drug release is dependent on its concentration from a device (Desai et al., 1966). Hixon-Crowell equation is used to describe the mechanism of drug release depending on change of shape and size of the device (Hixon et al., 1931). Higuchi's equation is based on drug release from insoluble matrix from insoluble polymeric system. It describes the time independent process based on Fick's law (Higuchi, 1963). Korsmeyer-Peppas mathematical equation is used to assess the mechanism of release (Peppas, 1985).

2.12 Size and Morphological Analysis

Optical microscope (Nikon, Japan) was used to measure particle size of different PCL microspheres. Scanning electron microscopy was used to analyze the surface properties of microspheres. The prepared microspheres were sprinkled on one side of the adhesive stub. The stub was then coated with conductive gold with JOEL-JFC 1600 auto coater and was examined under JOEL-JFC 6360 SEM for qualitative assessment of microsphere morphology.

3. RESULTS AND DISCUSSION

Figure 1 (a) presents the spectrum of PCL, venlafaxine and PCL microspheres. There is no new peak in the spectrum of drug microspheres. FTIR spectrum of PCL displays a characteristic absorption band of the carbonyl stretching mode around 1682 cm−1 (C=O), asymmetric stretching at 2951 cm−1 (CH2) and symmetric stretching at 2862 cm−1 (CH2). FTIR spectrum of venlafaxine is shown as Figure 1 (b), shows characteristic peak at 3330 cm−1 due to stretching of O-H. The peak at 2825 cm−1 is due to C-H stretch. Peak at 1208 cm−1 indicates C-O stretching vibration. Peak of C-O-C stretch shoulders at 1028 cm−1. Figure 1 (c), displays the spectrum of venlafaxine loaded PCL microspheres. Analysis of spectrum reveals that there is no new peak. Therefore, it can be concluded that PCL and venlafaxine are compatible, stable and no chemical interaction exists between them.

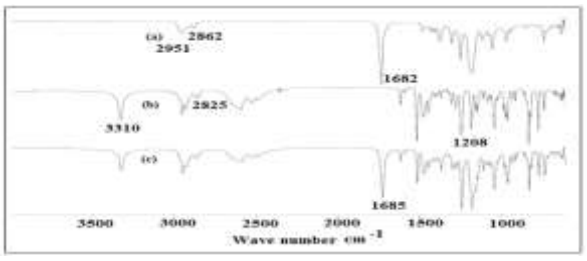

Figure 1: FTIR spectra (a) PCL (b) venlafaxine (c) PCL microspheres

PCL microspheres were spherical in shape and non-porous with smooth surfaces. Figure 2 describes SEM micrograph of P5. The particle size of microspheres increased on increasing quantity of PCL in formulations. Mean particle size was 163 ± 11.34, 171 ± 14.56, 189 ± 10.74, 207 ± 12.04 and 224 ± 11.48µm for P1, P2, P3, P4 and P5, respectively. Increase in particle size is justified by the fact that a thick wall is formed on increase of PCL ratio.

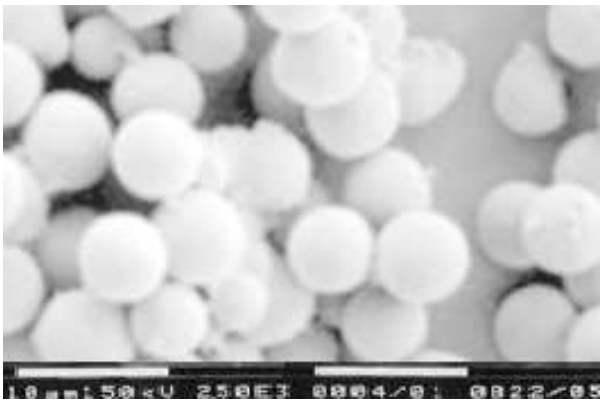

Figure 2: SEM micrograph of P5

Thermal studies are performed to evaluate compatibility and stability of new formulations. Thermal studies both DSC and TGA prove some increase in stability of venlafaxine loaded biodegradable PCL microparticles and ensures uniform distribution of drug at molecular level. DSC curves of PCL, venlafaxine and venlafaxine loaded microspheres have been shown in Figure 3 (a), (b) and (c), respectively. Similarly, TGA thermograms of PCL, venlafaxine and PCL microparticles are shown in Figures 4 (a), (b) and (c), respectively. There is an endothermic peak at 64°C in DSC curve of PCL, which corresponds to melting point of PCL. The peaks of venlafaxine at 235°C and 268°C correspond to melting and degradation endotherm, respectively. However, these endothermic peaks were absent or highly reduced in intensity in DSC curve of venlafaxine loaded PCL microspheres. This indicated greater stability and compatibility due to molecular dispersion of venlafaxine in amorphous form in microspheres. The DSC technique can provide qualitative and quantitative information about the physicochemical status of drug in microspheres, which is reported to be involved in the endothermic or exothermic process. The related thermal transitions include melting, recrystallization, decomposition and out gassing or a change in heat

capacity. DSC is useful to monitor different samples of same material to assess their similarities or differences or the effects of additives on the thermal properties of a material. Using the DSC analysis of drug, polymer and produced microspheres, the nature of drug inside polymer matrix can be assessed, which may emerge in solid solution, metastable molecular dispersion or crystallization. In order to identify the mechanism of sustained drug release, we first characterized the physical state of the drug within the microparticles. Samples were subjected for DSC studies. However, the melting peak was absent on the DSC thermograms of microparticles containing venlafaxine, indicating that the drug was dispersed in the microparticles as an amorphous form. This amorphous nature of the drug may have pronounced pharmaceutical significance as it could lead to increased solubility and finally to an improved biological activity (Jagadeesh *et al*., 2010).

Table 1: COMPOSITION OF PCL MICROSPHERES

Formulation	PCL (g)	Venlafaxine (g)	Corn oil (mL)	Span 85 (g)
P1	1.0	1.0	120	0.12
P2	1.5	1.0	120	0.12
P3	2.0	1.0	120	0.12
P4	2.5	1.0	120	0.12
P5	3.0	1.0	120	0.12

Table 2: MEAN VALUES OF % YIELD AND MICROMERITIC PROPERTIES OF MICROSPHERES

Sample	(%)yield	Entrapment efficiency (%)	Tapped density	Bulk density	Compressibility index	Hausner's ratio	Angle of repose
P1	91.88	64.67	0.38	0.27	11.37	1.14	25.27
P2	92.23	63.55	0.43	0.29	11.85	1.13	26.45
P3	91.11	69.22	0.41	0.31	10.59	1.13	25.05
P4	90.87	71.29	0.47	0.32	12.45	1.13	27.39
P5	92.76	70.81	0.51	0.34	13.43	1.11	27.81

Percent recovery of PCL microspheres was >90% for all formulations and was independent of PCL ratio. However, entrapment efficiency increased gradually from 64.67% to 70.81 from P1 to P5. Mean values of % yield and % entrapment efficiency are presented in Table 2.

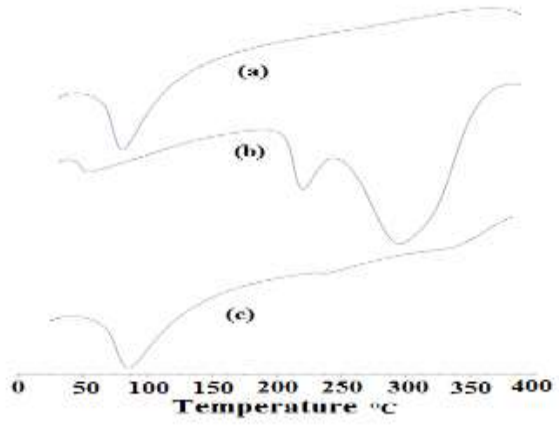

Figure 3: DSC curves of (a) PCL (b) venlafaxine (c) PCL microspheres

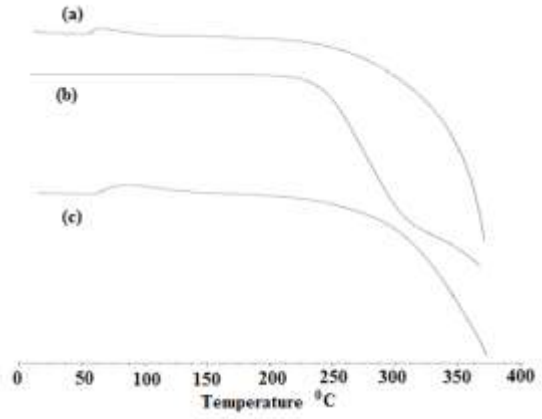

Figure 4: Thermograms of (a) PCL (b) venlafaxine (c)

PCL microspheres

The bulk properties of PCL microspheres have been presented in Table 2. All formulations of PCL microspheres showed good packing and free flowing characteristics.

Figure 5, describes the release pattern of new formulations. The drug release was fast and rapid in formulations with less quantity of PCL. However, there was a gradual reduction in initial burst release (69.53 % from P1), (62.37 % from P2), (55.45 % from P3), (53.76 % from P4) and (49.32 % from P5). Similarly, the sustained effect was increased up to 8 h for P5. The sudden and rapid initial release is attributed to high solubility of venlafaxine (572 mg/mL). As water approaches microspheres, water channels are produced. Drug is leached out suddenly from the surface of microspheres due to its high solubility. The burst effect was reduced by adding more quantity of PCL. High amount of PCL produce microspheres with thick wall and large size. Water has to diffuse a long distance to penetrate the interior surface of microspheres. Thick and hydrophobic PCL restricts free penetration of water into microspheres. Regression coefficients and release constants were calculated by linear regression analysis and slope of plot area, respectively. The release data when fitted to various model equations, showed highest linearity of regression coefficient for Higuchi model. The release data was suitably explained by Higuchi's model followed by first order release. The release of venlafaxine from insoluble, hydrophobic matrix was governed by time dependent diffusion based on Fick's law. The mechanism of release as calculated from Peppas equation suggests an anomalous diffusion.

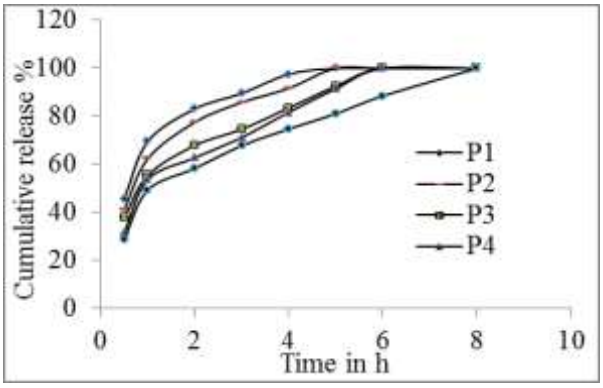

Figure 5: Release profile of PCL microspheres

4. Conclusion

In this work, we developed biodegradable microspheres of PCL for controlled release of a novel highly water soluble venlafaxine. The developed microspheres showed good packing and flow properties. The structure of microsphere was smooth and drug entrapped was in amorphous form as revealed by thermal analysis. The major and serious drawback associated with new formulations was initial burst release phenomenon. However, burst effect was minimized to some extent by increasing amount of PCL in microsphere formulations. The burst effect was > 49 % of entrapped drug even with the highest quantity of PCL in P5. P5 showed biphasic release behaviour. After initial burst, the release of venlafaxine was sustained up to 8 h. Initial burst effect is a great challenge for development of controlled release dosage form for highly soluble venlafaxine. New strategies are required to overcome the burst effect.

Conflict of Interests

Authors of this study declared no conflict of interests for this work.

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