AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

In vitro Comparative study of Venlafaxine Hydrochloride Sustained Release Formulation using different Lipidic Matrices Prepared by Melt Granulation Technique.

Gaurav S. Yeola[1], Dnyanesh B. Shelar[1], Pravin D. Chaudhari*[1]

1.Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune- 411018, Maharashtra, India.

ABSTRACT

The objective of this study was to investigate hydrogenated vegetable oil (Lubritab) and hydrogenated castor oil (HCO) as potential lipophilic binders in melt granulation process for the preparation of sustained release matrices of venlafaxine hydrochloride, a highly water soluble drug. The effect of concentration, type of polymer and method of preparation (direct compression of physical mixtures and melt granulation technique) were studied. Granules prepared by melt granulation method were evaluated for micromeritic properties, FT-IR, DSC, XRD and SEM. The compressed tablets were subjected to thickness, hardness, friability, mass variation test, drug content and in vitro release studies. The result of dissolution study showed that formulations containing drug: HCO (1:3 m/m) retarded drug release more than those containing drug: Lubritab (1:3 m/m) ratio. In conclusion, melt granulation technique was found to be more appropriate in retarding the release compared to compression of physical mixtures of drug and lipophilic binder. The study showed that HCO and Lubritab are the appropriate meltable binders that can be utilized as matrix-forming agent to sustained the release of highly water soluble drugs.

Keywords: sustained release, melt granulation, hydrogenated castor oil, hydrogenated vegetable oil

*Corresponding Author Email: gauravyeola@yahoo.com

Received 25 January 2013, Accepted 02 February 2013

Please cite this article in press as Chaudhari PD *et al.*, In vitro Comparative study of Venlafaxine Hydrochloride Sustained Release Formulation using different Lipidic Matrices Prepared by Melt Granulation Technique . American Journal of PharmTech Research 2013.

INTRODUCTION

Venlafaxine HCl is a unique antidepressant that differs structurally from other currently available antidepressants[1]. venlafaxine and its active metabolite o-desmethylvenlafaxine (ODV), inhibit the neuronal uptake of norepinephrine, serotonin and to a lesser extent dopamine[2,3] but have no mono amine oxidase inhibitory activity and low affinity for brain muscarinic, cholinergic, histaminergic or alpha adrenergic receptors[4,5]. The steady state half lives of venlafaxine and ODV are 5 and 11 h, respectively, necessitating its administration, two or three times daily so as to maintain adequate plasma levels of drug[6]. Makhija and Vavia attempted the development of sustained release dosage form of venlafaxine in the form of tablets[7].

The matrix system is commonly used for manufacturing sustained release dosage forms. A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to matrix concept. Waxes, hydrophobic and water insoluble materials, which are potentially erodable, have been used in forming sustained release formulation.

Recently several systems have been developed to produce sustained release formulations using melt granulation technique[8]. These include use of hydrogenated castor oil for preparation of controlled release tablets[9], compritol 888 ATO for preparation of matrix pellets[10]. Melt granulation or thermoplastic granulation is known as a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at a relatively low temperature. When melted, the action of the binder is similar to that occurring in a wet granulation process. As a “one-step” operation, melt granulation offers several advantages compared to conventional wet granulation since the liquid addition and the subsequent drying phases are omitted. Moreover, it is also a good alternative to the use of solvents, in terms of cost and safety, when granulating water-sensitive materials. Thus the process is less consuming in terms of time and energy compared to other methods. Numerous hydrophilic or fatty excipients having a melting range between 50° C and 100° C, such as polyethylene glycols, waxes, stearic acid are the typical examples of meltable binders. By selecting lipophilic binders, melt granulation can be means of producing sustained release granules, pellets, or matrix tablets[11,12].

The objective of the present study was to prepare oral sustained release venlafaxine HCl matrices, to evaluate the effect of method of preparation (direct compression of physical mixtures versus melt granulation technique). The effect of two different lipophilic binders (hydrogenated vegetable oil and hydrogenated castor oil) at different concentration was also studied.

MATERIALS AND METHDS

Materials

Gift sample of venlafaxine hydrochloride (VFX) was obtained from Cipla Ltd. India Kurkumb, Pune and microcrystalline cellulose (MCC) provided by S. D. Fine Chemicals, India was used as the diluent. Hydrogenated castor oil and hydrogenated vegetable oil (Lubritab) were supplied by Henkel, Germany and Penwest Pharma, USA respectively. They were used as low melting lipophilic binders with the melting points of 84 °C and 63 °C respectively. Both of these fatty excipients occur as fine white to slightly yellow free-flowing powders. All other chemicals were of analytical grade.

Preparation of matrices by melt granulation

Formulation batches are shown in Table 1.

Table I. Formulations containing different lipidic matrices concentrations

Ingredients	F-I	F-II	F-III	F-IV	F-V	F-VI
venlafaxine Hydrochloride	85	85	85	85	85	85
Hydrogenated Vegetable oil	85	170	255	-	-	-
Hydrogenated castor oil	-	-	-	85	170	255
MCC	224	140	55	224	140	55
Magnesium stearate	4	4	4	4	4	4
Aerosil-200	2	2	2	2	2	2
Total Tablet weight (mg)	400	400	400	400	400	400

The meltable binder was melted in porcelain dish on a water bath maintained at constant temperature for different meltable binders as per their melting points. Venlafaxine HCl was gradually added to the molten wax with continuous stirring. The molten mixture was allowed to cool and solidify at room temperature. The drug was present in its solid form within the molten mixture. The solidified mass was pulverized in mortar and sieved through a 1.18 mm screen. The granules which passed through 1.18 mm sieve were mixed with microcrystalline cellulose, magnesium stearate, Aerosil – 200 and compressed into a flat-faced tablets using KBr press at one ton pressure for the batch of 100 tablets. On the other hand the physical mixtures of drug and meltable binder were compressed into tablets.

Characterization of granules:

The granules were subjected to testing for angle of repose, bulk density, and particle size distribution, FTIR, DSC, XRD, and SEM. The tablets were evaluated for thickness (n = 20), mass variation (n = 20), hardness (n =20), drug content (n = 6), friability (n = 20) and *in vitro* dissolution (n = 3).

The angle of repose of granules was determined by the funnel method. The accurately weighed

granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [13] :

$\tan \theta = h/r$

where h and r the height and radius of powder cone.

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 5 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own mass onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued was until no further change in volume was noted.

The compressibility of the granules was determined by Carr's compressibility index (CI)[15]:

CI (%) = [(TBD-LBD) X 100] / TBD

The particle size distribution of granules was evaluated by sieve analysis method using a vibrating shaker and six standard sieves in the range of 75 -1200 µm. The fractions were collected and weighed[16].

Infrared spectroscopy

Fourier transform- infrared (FT-IR) spectra of drug, meltable binders and granules were obtained using bromide as pellet making substance (Model 8400 S, Shimadzu, Japan). The spectra were scanned over the wave number range from 3600 – 400 cm^{-1}.

Differential scanning calorimetry

Thermograms of venlafaxine HCl, VFX-Lubritab and VFX-HCO granules were obtained using a Mettler-Toledo DSC 821[e], Switzerland instrument equipped with an intracooler. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The powder samples of granules was hermetically sealed in an aluminum pan and heated at constant rate of 10 ^{o}C/min, over a temperature range of 30 ^{o}C to 250 ^{o}C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 $mLmin^{-1}$.

X-ray diffractometry

The X-ray diffraction patterns were also determined for granules prepared by melt granulation. Samples were exposed to monochromatic nickel-filtered copper radiation (40kV, 40mA) in a wide angle X-ray diffractometer (Siemens D 5000, Germany) with 2θ angle between 5° and 60°.

Scanning electron microscopy

The granules were coated with a thin gold-palladium layer using a sputter coater unit JFC 1100

(Jeol, Japan) and the surface topography was performed with a JSM 840 (Jeol, Japan) scanning electron microscope (SEM).

Evaluation of Tablets

Thickness

The thickness and diameter of tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used, and average values were calculated.

Weight variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method[17] .

Drug content

Five tablets were weighed individually, and these tablets were crushed in mortar. From which drug equivalent to 10 mg of powder was taken, to this 10 ml of distilled water was added. The mixture was heated to melt (as per melting point of meltable binders) and allowed to cool to room temperature. The lipid was solidified and drug solution was filtered through 0.45µ membrane filter [18]. The absorbance was measured at 226.5nm after suitable dilution. The drug content was determined.

Hardness and friability

For each formulation, the hardness and friability of 20 tablets were determined using the Monsanto harness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Lab Hosp., India), respectively.

In Vitro Release Studies

In vitro drug release studies from the prepared matrix tablets were conducted for period of 24 hours using USP XXIII apparatus type II (Veego DA 6D, India) under sink condition. The dissolution medium consist of the phosphate buffer pH 6.8 (900ml), maintained at 37°C±0.5°C; paddle speed 100 rpm. At every one hour interval samples of 10ml were withdrawn from dissolution medium and replaced with fresh medium to maintain volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 226.5nm using UV spectrophotometer (Shimadzu 1601, Japan). The release studies were conducted in triplicate. Drug dissolved at specified time periods was plotted as percent release versus time (hours) curve.

Data analysis

To analyze the mechanism of drug release from the matrix tablets, the in vitro release data were fitted into the various release equations and kinetic models such as first order, zero order, Higuchi and Peppas.

RESULTS AND DISCUSSION

Granulation is the key process in the production of many dosage forms involving the sustained release of a drug from coated or matrix type particles. Physical properties of granules such as surface area, shape, hardness, surface characteristics and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation[19]. The granules of different formulations were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD) and compressibility index (Table 2). The results of angle of repose and compressibility index (%) ranged from 13.52 – 17.65 and 14.79 - 21.05% respectively. The results of LBD and TBD ranged from 0.387 to 0.699 g/ml and 0.461 to 0.836 g/ml respectively. The result of angle of repose (<20) indicate excellent flow properties of granules (15). This was further supported by lower compressibility index values. Generally, compressibility index values up to 18% result in good to excellent flow properties. All these results indicate that the granules possessed satisfactory flow properties and compressibility.

Table II. Properties of the Granules.

Formulation	Angle of Repose	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility index (%)
F-I	16.24±0.02	0.699±0.03	0.873±0.06	19.93±0.03
F-II	17.65±0.02	0.435±0.04	0.551±0.02	21.05±0.02
F-III	15.63±0.03	0.398±0.03	0.481±0.03	17.24±0.04
F-IV	14.41±0.02	0.669±0.02	0.836±0.04	19.97±0.04
F-V	13.16±0.02	0.415±0.03	0.501±0.04	17.16±0.03
F-VI	13.52±0.04	0.424±0.03	0.520±0.03	18.46±0.02

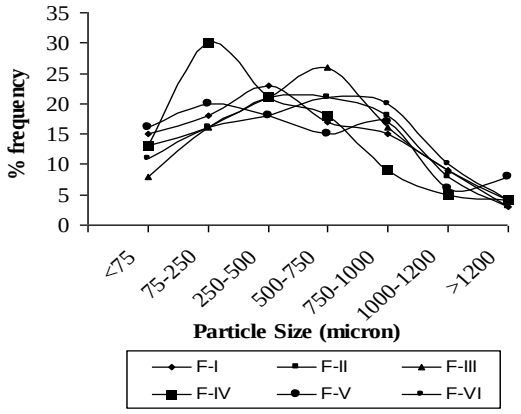

Figure 1. Particle size distribution of venlafaxine HCl granules obtained by melt granulation using Lubritab and hydrogenated castor oil.

Particle Size Distribution

A number of reports have been published[20] showing that process variables and amount of binder have a great effect on the characteristics of the granules obtained by melt granulation. Figure 1

show the particle size distribution of venlafaxine HCl granules prepared using lipophilic binder in different concentrations i.e. drug: lipophilic binder in the ratio of 1:1, 1:2, 1:3 m/m by melt granulation technique. The amount of fine powder (size <75 µm) and the amount of big lumps (size > 1000 µm) are low. The main fraction was 250 – 1000 µm and maximum percentages of granules were present in this size range.

Infrared Spectroscopy

IR spectrum of venlafaxine HCl (Figure 2) indicated characteristics peaks at wavenumbers 1513, 1243, 1179 cm^{-1}. Meltable binder peak was broad at 3331 cm^{-1} and after mixing becomes sharp, it might be speculated that the intermolecular H-bonding from meltable binder was removed. The IR spectra of the samples showed, lack of significant interaction between drug and polymer, as all characteristic bands of venlafaxine HCl were observed in IR spectra of melt agglomerates.

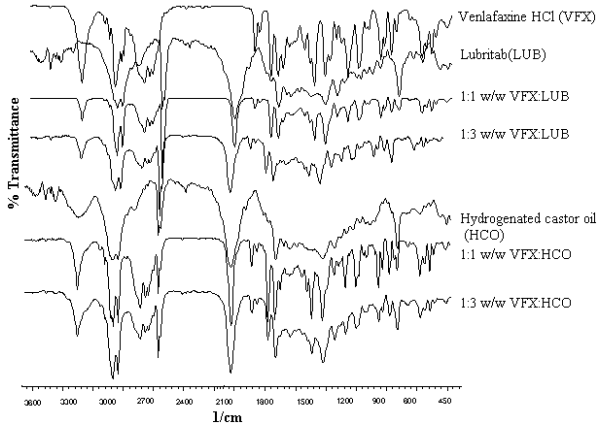

Figure 2. Infrared spectroscopy of venlafaxine HCl (VFX), Lubritab (LUB), Hydrogenated castor oil (HCO) and melt granules of drug: lipophilic binder in different ratios.

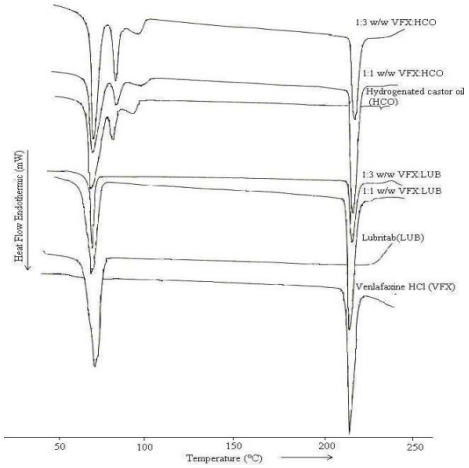

Figure 3. . Differential scanning calorimetric curve of venlafaxine HCl (VFX), Lubritab (LUB), Hydrogenated castor oil (HCO) and melt granules of drug: lipophilic binder in different ratios.

Differential Scanning Calorimetry

Figure 3 shows the DSC thermograms of venlafaxine HCl, Lubritab and granules obtained by melt granulation method. DSC curve of pure venlafaxine HCl showed a single endothermic peak at 214.81°C, due to melting of the drug. Lubritab showed an endothermic peak at 61.87°C.

The DSC curves of melt granules showed the endothermic peak at 61.38°C and 61.05°C respectively for VFX: Lubritab (1:1 and 1:3 m/m ratio). There is slight shift of endothermic peak of drug i.e. 210.51°C and 210.08°C was observed than that of pure drug which shows there is no interaction between drug and Lubritab.

DSC heating curves of hydrogenated castor oil showed an endothermic deviation of baseline at approximately 45°C, while the melting was only ended at 85°C (Figure 3). Hydrogenated castor oil showed three different endothermic peaks at 56.17°C, 68.36°C and 80.48°C. There was slight change in endothermic peak of venlafaxine HCl i.e. 211.08°C and 210.16°C for VFX: HCO (1:1 and 1:3 m/m ratio) respectively than that of the pure drug in melt granules. As concentration of lipophilic binder increases the intensity of drug peak decreases due to dilution effect as observed in DSC curves shown in Figure 3.

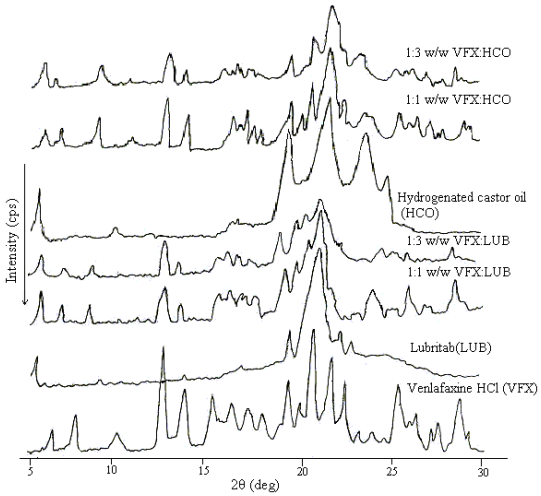

Figure 4. X-ray diffraction patterns of venlafaxine HCl (VFX), Lubritab (LUB), Hydrogenated castor oil (HCO) and melt granules of drug: lipophilic binder in different ratios.

X-Ray Diffractometry

Diffractogram of untreated venlafaxine HCl showed that the drug was crystalline, as demonstrated by numerous sharp and intense peaks (Figure 4). Granules prepared with varying ratios of VFX: Lubritab (1:1 and 1:3 m/m) showed no potential interaction between these two. However at 1:3 m/m ratio of VFX: Lubritab, the XRD pattern closely resembles with that of pure

Lubritab (Figure 4). This might be due to efficient coating of Lubritab on venlafaxine HCl, since the proportion of Lubritab in the granulate was very high. Similar observations were depicted in case of VFX: HCO (1:1 and 1:3 m/m) ratio, wherein the XRD pattern of 1:3 m/m granulate was similar to that of neat HCO.

Scanning Electron Microscopy

SEM of pure venlafaxine HCl showed rod shaped crystals (Figure 5). Photomicrograph of Lubritab showed presence of porous structure along with few spikes. At 1:1 m/m ratio of drug: lubritab partial covering of drug crystals was observed while at 1:3 m/m ratio of drug: lubritab majority of drug crystals were coated by Lubritab as can be seen from Figure 6. The coating of drug crystals with Lubritab is due to melt granulation process wherein Lubritab was melted and drug was mixed with it by manual kneading.

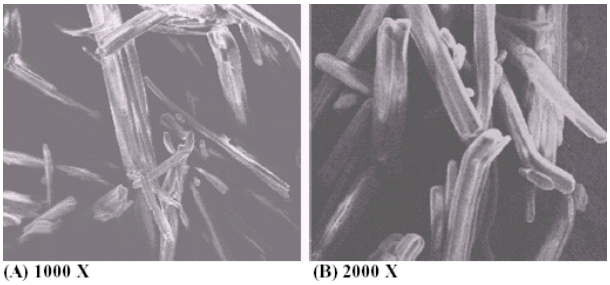

Figure 5. SEM photographs of pure venlafaxine HCl at magnification of (A) 1000 X and (B) 2000 X

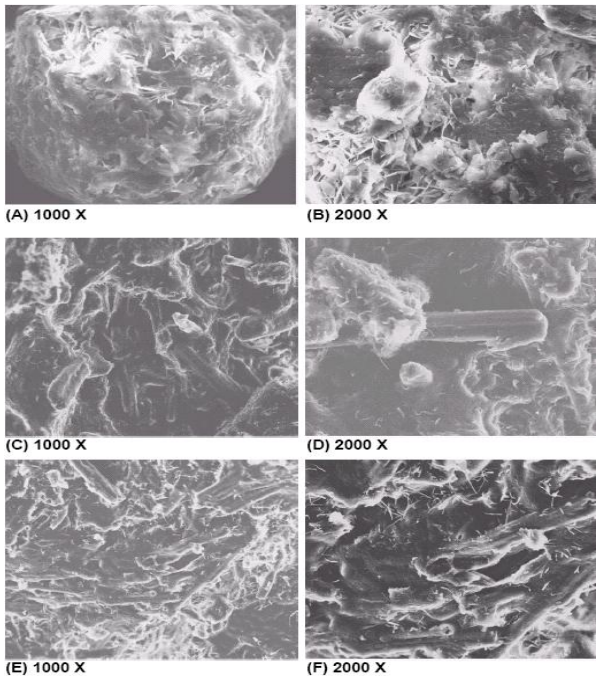

Figure 6. SEM photographs of Lubritab (LUB) [(A) at1000 X and (B) at 2000 X], 1:1 m/m VFX: LUB [(C) at 1000 X and (D) at 2000 X], 1:3 VFX: LUB [(E) at 1000 X and (F) at 2000 X]

Also in case of hydrogenated castor oil (HCO) the extent of polymer coating of drug crystals was high at 1:3 m/m ratio of drug: HCO as compared to 1:1 m/m ratio (Figure 7).

For both the polymers viz. Lubritab and HCO the coating of drug crystals did not result in change in its shape, although the extent of coating varied according to Drug: lipophilic binder ratios.

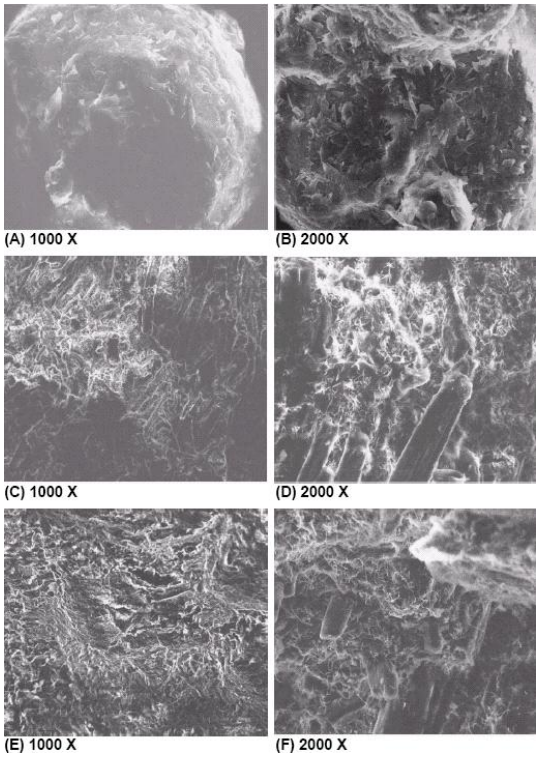

Figure 7. SEM photographs of Hydrogenated castor oil (HCO) [(A) at1000 X and (B) at 2000 X], 1:1 m/m VFX: HCO [(C) at 1000 X and (D) at 2000 X], 1:3 VFX: HCO [(E) at 1000 X and (F) at 2000 X]

The tablets of different formulations were subjected to various evaluation tests such as thickness, uniformity of weight, drug content, hardness, friability and in vitro dissolution (Table 3). The thickness of the tablets ranged from 2.70 to 2.71 mm. Drug content was found to be uniform among different batches of the tablets and ranged from 95.77 and 98.88. The hardness and percentage friability of the tablets of all batches range from 6.1 to 10.33 kg/cm^2 and 0.50 to 0.66 % respectively. All the formulations showed uniform thickness. In a weight variation test, the Pharmacopeial limit for the percentage deviation for tablets of more than 250 mg is ±5% [17]. The average percentage deviation of all tablet formulations was found to be within the above limit; hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 95%. As the concentration of lipophilic binder increased, cold

welding of waxes increased in melt granules, and therefore tablet hardness increased. Also hardness increased proportionately with increase in melting point of lipophilic binder i.e. from Lubritab (M.P.63°C) to HCO (M.P.84°C).

In vitro dissolution test

The results of in vitro dissolution studies of formulations F-I, F-II and F-III, composed of hydrogenated vegetable oil and F-IV, F-V and F-VI composed of hydrogenated castor oil as a carrier (drug: lipophilic binder 1:1, 1:2 and 1:3 m/m ratio) prepared using melt granulation technique, are shown in Figure 8.

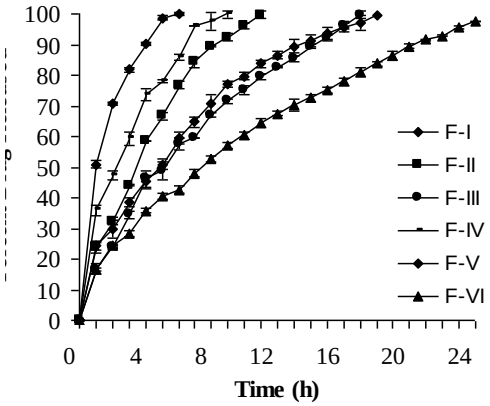

Figure 8. Effect of increasing the drug: meltable binder ratios (1:1, 1:2, 1:3 m/m) on the release of venlafaxine HCl from the matrices prepared by melt granulation.

Formulations F-I, F-II and F-III released 100.12±0.65%, 99.67±1.32% and 99.47±1.06% of venlafaxine HCl at the end of 6 hours, 11 hours and 17 hours, respectively.

Formulations F-IV, F-V and F-VI released 99.88±1.22%, 99.52±2.44% and 97.50±0.18% of venlafaxine HCl at the end of 9 hours, 18 hours and 24 hours respectively.

From Figure 8 it can be observed that for all the matrices drug release was inversely proportional to level of release retarding matrix former present in the system i.e. the rate and extent of drug release decreased with increase in total lipid content of matrix. In order to study the effect of method of preparation of matrices on release characteristics of venlafaxine HCl from sustained release tablets, two methods were studied i.e. melt granulation and physical mixtures by direct compression. Formulation F-III and F-VI were prepared by both the methods and studied for in vitro release characteristics. Figure 9 showed comparative release profiles of matrices prepared by direct compression of physical mixtures and matrices prepared by compression of granules by melt granulation. The results indicated that from matrices prepared by direct compression of physical mixtures F-III PM and F-VI PM released 100% drug at the end of 2 hours and 9 hours respectively.

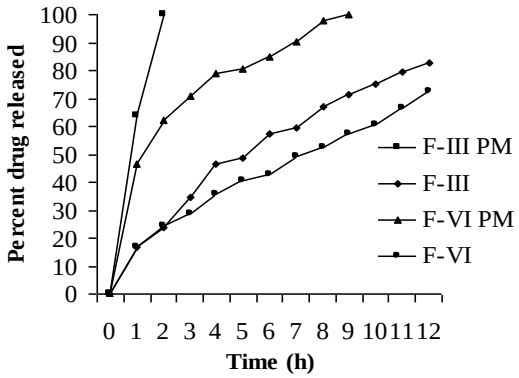

Figure 9. Release profiles of venlafaxine HCl from matrices made by direct compression of physical mixtures and melt granulation technique.

The results of dissolution studies indicated that F-I, F-II, F-III and F-IV, F-V, F-VI matrix tablets did not show any disintegration after 24 hours of dissolution period irrespective of polymer content. It was reported that use of hydrogenated vegetable oil as a lipophilic binder because of its moderate melting point 63°C (21). Drug release was faster from Lubritab than HCO as melting point increases from 63°C to 84°C. At 75% (1:3m/m ratio) polymeric content 99.67% and 97.50% of venlafaxine HCl was released from Lubritab and HCO at the end of 17 hours and 24 hours respectively. On the other hand 50% (1:1m/m ratio) polymeric load, 100% and 99.88% of venlafaxine HCl was released at the end of 6 and 9 hours from Lubritab and HCO. The fact can be reasoned on the basis of polymeric nature and mechanism by which these polymers release drug in the surrounding medium. HCO imparted highest retarding effect and extensively retarded drug release. This finding was in accordance with work carried out by Tiwari et al. HCO is extremely hydrophobic in nature with lower wettability. Total release of drug from such matrix system was not possible since a certain fraction of dose is coated with impermeable wax film. It is also postulated that, in the absence of additives, drug release is prolonged and nonlinear from wax matrix systems. As our formulation contain MCC which forms pores and cracks by facilitating solvent front penetration i.e. channeling and elevation of drug release due to which higher release of drug from wax matrices was observed.

HCO is a very good retardant due to its high melting point that avoids occurrence of sticking to punches during tabletting and allows for maintenance of tablet integrity even after complete dissolution of drug while release rate was modulated by varying its concentration in matrix tablet.

Physical mixtures showed disintegration of tablets rapidly and showed faster release as lipophilic binder was not melted during granulation and therefore its binding and sustained release

properties were less effective. Hydrogenated castor oil was found to be a good retardant since it forms thin coating on surface of drug particle. The slow release of drug could be due to the formation of uniform coating on individual drug particles by hydrophobic polymer during melt granulation. The initial burst release was observed which might be due to drug which was not coated during melt granulation i.e. surface free drug. The melting point, HLB value, lipophilicity and matrix integrity are the important factors determining drug release properties from lipidic matrices prepared by melt granulation.

To explore the release pattern, results of the *in vitro* release data of formulation III and VI were fitted to the Korsmeyer and Peppas equation ($Mt/M\alpha = k\ t^n$, where Mt/Mα is the fraction of drug released after time t; k is the rate constant and *n* is the diffusional exponent) (22) which characterize the transport mechanism. The value of *n* was 0.5570 (R^2 = 0.9822) and 0.5244 (R^2 = 0.9783) for formulations III and VI respectively indicating release governed by anomalous transport (Non Fickian) diffusion.

The release was higher from the matrices made by direct compression of physical mixtures as compared to matrices made by compression of granules by melt granulation. The result was attributed to this formation of coating of lipophilic binder over drug particles is more uniform in melt granulation technique than matrices prepared by direct compression.

CONCLUSION

The study showed that both hydrogenated vegetable oil and hydrogenated castor oil are potential lipophilic binders that can be utilized as matrix forming agent to prolong the release of water soluble drug such as venlafaxine HCl. Preparation of matrices by compression of hot melt granules were found to be more effective than compression of physical mixtures in controlling the release of drug. It is evident from the results that a hydrophobic matrix prepared by HCO is better system for sustained release of venlafaxine HCl.

ACKNOWLEDGEMENT

Authors thank Cipla Ltd., Pune, Penwest Pharma and Henkel, Germany for providing gift samples of venlafaxine HCl, hydrogenated vegetable oil and hydrogenated castor oil respectively.

REFERENCES

1. Holliday SM, Benfield P. Venlafaxine: a review of its pharmacology and therapeutic potential in depression, Drug. 1995; 49(2): 280-294.

2. Haskins JT, Moyer JA, Muth EA, Sigg EB. Inhibition of noradrenergic neuronal activity by the novel bicyclic compounds, Wy-45,030 and Wy-45,881. Soc. Neurosci. Abstr. 1984;10: 262.
3. Muth EA, Haskins JT, Moyer JA, Husbands GE, Andree TH, Biochemical, neurophysiological and behavioural effects of Wy-45,233, its enantiomers and other identified metabolites of the antidepressant venlafaxine, Drug Dev. Res. 1991;23: 191-199.
4. Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain receptors: focus on newer generation compounds, Psychopharmacology. 1994;114: 559-565.
5. Muth EA, Haskins JT, Moyer JA, Husbands GE; Nielsen ST, Sigg EB. Antidepressant biochemical profile of the novel tricyclic compound Wy-45,030, an ether cyclohexanol derivative, Biochem. Pharmacol. 1986; 35: 4493-4497.
6. Troy SM, Parker VD, Fruncillo RJ, Chiang ST. The pharmacokinetics of venlafaxine when given in a twice daily regimen, J. Clin. Pharmacol. 1995; 35: 404-409.
7. Makhija SN, Vavia PR. Once daily sustained release tablets of venlafaxine, a novel antidepressant, Eur. J. Pharm. Biopharm. 2002; 54: 9-15.
8. Royce A, Suryawanshi J, Shah U, Vishnupad K. Alternative granulation technique: melt granulation, Drug Dev. Ind. Pharm. 1996; 22 (9,10): 917-924.
9. Tiwari SB, Murthy TK, Pai MR, Mehta PR, Chowdary PB. Controlled release formulation of Tramadol hydrochloride using hydrophilic and hydrophobic matrix system, AAPS PharmSciTech. 2003; 4(3): article 31.
10. Hamdani J, Moes AJ, Amighi K. Physical and thermal characterisation of precirol and compritol as lipophilic glycerides used for the preparation of controlled- release matrix pellets, Int. J. Pharm. 2003; 260: 47-57.
11. Evrard B, Delattre L. Influence of melting and rheological properties of fatty binders on melt granulation process in high shear mixer, Drug Dev. Ind. Pharm. 1999; 25(11): 1177-1184.
12. Schaefer T, Holm P, Kristensen HG. Melt granulation in a laboratory scale high shear mixer, Drug Dev. Ind. Pharm. 1990; 16(8): 1249-1277.
13. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, eds. Tutorial Pharmacy, New Delhi: CBS publishers and distributors, India 1986: 211-233.
14. Shah D, Shah Y, Rampradhan M. Development and evaluation of controlled release diltiazem hydrochloride microparticles using cross-linked poly (vinyl alcohol), Drug Dev. Ind. Pharm. 1997; 23(6): 567-574.

15. Aulton ME, Wells TI, Pharmaceutics: The science of dosage form design. London: Churchill Livingstone, England 1988.
16. Martin A. Micromeritic. In Martin A, ed. Physical pharmacy. MD, Baltimore: Lippincott Williams and Wilkins, 2001: 423-454.
17. Pharmacopoeia of India. New Delhi: Ministry of health and family welfare, Government of India, Controller of publications, 1996.
18. Shimpi S, Chauhan B, Mahadik KR,Paradkar A. Preparation and evaluation of diltiazem hydrochloride-gelucire 43/01 floating granules prepared by melt granulation. AAPS PharmSciTech. 2004;5(3): article 43.
19. Banker GS, Anderson LR. Tablets. In: Lachman L, Liebermann HA, Kanig JL. eds. The theory and practice of industrial pharmacy, Mumbai: Varghese publishing house, India 1987: 293-345.
20. Passerini N, Albertini B, Marisa L, Cavallari C, Rodriguez L. Preparation and characterisation of ibuprofen-poloxamer 188 granules obtained by melt granulation, Eur. J. Pharm. Biopharm. 2002; 15: 71-78.
21. Evrard B, Delattre L. In vitro evaluation of lipid matrices for the development of a sustained release sulfamethazine bolus for lambs. Drug Dev. Ind. Pharm. 1996; 22(2): 111-118.
22. Costa P, Labo J S M S. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 2001;13: 123–133.