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Original Research Article

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The influence of hot melt subcoat and Polymer coat combination on highly water soluble sustained release multiparticulate formulation.

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Abstract

The purpose of this study was to develop and optimize oral controlled-release formulations for highly water soluble model drug Venlafaxine hydrochloride using a combination of hot-melt subcoatings based coating polymer and aqueous polymer coating. Hot melt subcoating was achieved by centrifugal granulator. For the polymer coating, Acrylate-based (Eudragit RS 30D and Eudragit NE 30D), were used. Furthermore polymer coating, the pellets were evaluated with respect to their ability to modulate the in-vitro release of a highly water soluble compound. By using hot melt subcoating, the polymer coating level of pellets was reduced by half to obtain sustained release profile. In this study, the release profile of pellets was found to be optimum at a 4% level of hot melt subcoating and 15 % level of Eudragit® NE30D polymer coating combination, consequently meeting the desired responses. The release profile of the pellets prepared by this technique satisfied the first order plot with (R sq =0.9434) indicating the release of water soluble drug from porous matrices. By means of this hot-melt subcoating and polymer coating combination, sustained-release pellets containing venlafaxine hydrochloride were successfully prepared.

Keywords: Pellets; Controlled release dosage form; Hot melt coating; polymer coating.

Introduction

The multiunit controlled release dosage forms are usually manufactured by coating the drug-loaded pellets or granules with gastrointestinal fluid-insoluble polymers . The drug release is controlled by diffusion through the pores of polymer film. The coating of particulates such as powders, granules, pellets and tablets to produce controlled release dosage form is becoming increasingly popular, mainly due to the advances in coating technologies as well as availability of new coating materials[1].

At present, pellets containing drugs with highly water soluble property are prepared by the melt pelletization process [2], the natural polymer and cross-linking technique and polymer subcoating. To control the release currently, sustained-release method includes water-insoluble polymer coating such as ethyl cellulose dispersion, acrylate based dispersion, ion exchange resins, water insoluble or soluble matrix (i.e., stearic acid or HPMC), and osmotic agents forming osmotic pump[3,4,5]. However, the technique mentioned above can be employed in specific dosage forms or active ingredients with specific property. Extremely water soluble drugs needed higher polymer coating levels than poorly soluble ones, because of the migration during the application of the aqueous polymer dispersion [6]. This may create pores or channels on the surface or inner part of the pellets during dissolution. For compounds with this property, higher coating levels are required to prevent premature drug release.

But, the hot-melt coating techniques do not necessitate the usage of solvents and show promising function in taste masking, gastric resistance, acid resistance, sustained release and bioavailability enhancement, based upon type of coating polymer[7]. In order to control the release of extremely water soluble drug lipophilic subcoat has been proposed [8-10]. In this study, instead of polymeric subcoating, melt subcoating was applied to retard drug release. It functions as a wall between the polymers coated layer and the drug-loaded pellets, and is projected to reduce media penetration throughout the dissolution [11]. The use of wax in melt coating is advantageous because wax is inert to most pharmaceutical active compounds and also having controlled release properties[12,13](. The additives, cellulose-based or acrylate-based polymers, were investigated as the rate controlling substances.Therefore, in the present work, cetosteryl alcohol melt subcoating was carried out using a centrifugal granulator, where the cetosteryl alcohol was sprinkled through the volumetric feeder. Subsequently, water insoluble polymers, acrylate-based (Eudragit RS 30D and Eudragit NE 30D), were used for coating the pellets using fluidized bed technique. Although Eudragit products are true latex with low Tg's, particle coalescence at room temperature is still slow and incomplete, necessitating accelerated curing conditions and the incorporation of water-soluble additives Altogether, all these polymers efficiently encapsulates pellets to control drug release.

In conclusion, The main purpose of this study is to investigate the effectiveness of the combination of melt subcoating and polymer coating and to screen the water insoluble polymer coating to control the drug release of an extremely water soluble agent. In addition, the hot-melt subcoating can enhance the function of polymer coating as well as the roundness of pellets, which can be confirmed by scanning electron microscope (SEM) photographs. The mechanism of drug release from pellets prepared by the combination of hot-melt subcoating and polymer coating was approached.

Materials and Methods

Materials

The following chemicals were obtained from commercial suppliers and used for the experiment:- Venlafaxine hydrochloride (Arti Drugs India), Microcrystalline cellulose (Avicel PH 101, FMC biopolymer Nederland), Hydroxy propyl cellulose (L-HPC, Shin-Etsu Chemical, Japan), all of EP standard. Purified water was used as a liquid binder. Talc (Guangxi Yulin Talc Factory) was used as anticohesive agent, and TEC as plasticizer (Indo-Nippon Chemical Co. Ltd. Mumbai). The subcoating material cetosteryl alcohol was procured from Cognis India. The polymer coating material, Acrylate-based dispersions Eudragit RS 30D and Eudragit NE 30D were procured from Evonik, Mumbai India.

Core Pellets Preparation

Pellets (0.8 – 1.1 mm diameter) containingVanlafaxine Hydrochloride(as model drug), Avicel PH101 and HPC were prepared by extrusion and spheronization using a bench top laboratory extruder model-MG 55 and spheronizer model QJ 230 T-1 (Fuji Paudal Co. Ltd, Tokyo Japan). A wet mass was prepared from the powder mixture before extrusion by using water as granulating fluid. The spheronised pellets were dried using Fluidised Bed Drier (Retsch Gmbh & Co., Haan Germany, model-TG 100) operating at 60^0C for 20 min in 2 sets of air speeds, initially minimum and then increased to avoid the fragmentation of pellets.

Melt Sub coating using centrifugal granulator

In order to control the release of Vanlafaxine HCl, which is extremely water soluble, hot melt sub coating technique was used. Cetosteryl alcohol (melting point 48 ^{0}C) was selected as wax for melt subcoating at the level 2%, 4% and 6%. Hot melt coating technique is defined as the application of a fine layer of coating material in molten state over the substrate.

The wax melt subcoating was performed on centrifugal granulator (Granurex Freund GX-20, Freund Industrial Co., Ltd., Tokyo, Japan A centrifugal granulator has a rotating friction plate instead of a screen at the bottom of the product container. The inlet air was passed through an air gap between the rotating plate and the wall of the product container. The inlet temperature was set at 60 0C which was slightly higher than the melting point of cetosteryl alcohol and the outlet temperature was 40^0C. The movement of the particles in the equipment is helical and is the result of the centrifugal force from the rotating plate which tends to push the material towards the wall of the processing chamber in addition to the fluidizing force from the air stream through the gap which avoids particle sticking. However, the force of gravity allowed the product to fall towards the centre of the rotor plate. Heating was continued until the bed temperature of the particles was above 550C. At this time, cetosteryl alcohol was added to the rotary fluidized bed processor. The addition of cetosteryl alcohol was controlled through volumetric feeder and the weight gained was due to the percentage buildup of the pellets from the core pellets. After all the cetosteryl alcohol was added, 1% talc was added to avoid particle aggregation because it acts as an anticohesive agent.

Polymer coating

The release of drug substance from the reservoir system depends on the thickness of polymer coating (11). In order to determine the coating level needed for obtaining desired controlled release, pellets were coated in different weight gains (10% to 20% w/w) of solid polymer and samples of pellets were removed at 10%, 15 % and 20 %weight gain increments. Experiment lay out is mentioned in table 1.

Since many polymers used for controlled drug release are water-insoluble, they were traditionally applied from organic solutions. The disadvantages of this process are explosion / flammability hazards, environmental considerations, risk of residual solvents in the polymer film and the higher viscosity of polymer solutions. As an alternative, aqueous dispersion of the polymers has been developed. Polymer dispersion spreading on the surface of the pellets forms a plastic film coating. In this study, Acrylate-based Eudragit RS30D &Eudragit NE30D polymers were selected for coating. Eudragit RS30D and Eudragit NE30D are pH independent and insoluble, but due to their swelling in physiological media, are particularly well suited for controlling the drug release. Eudragit RS30D dispersion was prepared using TEC as plasticizer whereas no plasticizer was required to prepare polymeric dispersion of Eudragit® NE30D, due to its soft and flexible nature. However, talc was used as anticaking agent The polymer dispersion was sprayed on 500 g pellets, which had already been subcoated with 4 % cetosteryl alcohol. These pellets were then transferred to the fluidized bed coater (GPCG 1; Wurster insert; Glatt GmbH, Binzen, Germany) for sustained release coating. Final weight gain of 20% was targeted, but sampling was also performed at lower coating levels 10% and 15%. The process parameters were as follows: product temperature 23–25 C, air flow rate 80–90 m^3/h; spray rate 7 g/min, atomizing air pressure 2.0 bar; and spray nozzle diameter 1.0 mm. After coating, the pellets were dried for 10 minutes and subsequently cured.

Table 1 Experiment matrix

Trial	Type of Polymer (X1)	% Coat of polymer (X2)
RT1	Eudragir RS 30D	10
RT2	Eudragir RS 30D	20
RT10	Eudragir RS 30D	15
RT11	Eudragir NE30D	10
RT4	Eudragir NE30D	15
RT5	Eudragir NE30D	20

Dissolution studies

The In vitro dissolution of all the coated pellets was determined using the USP apparatus I (Electrolab TDT 08L, India). The test was performed in 900 ml 0.1N HCl as the dissolution medium with the temperature maintained at 37.0 ± 0.5 C, while the stirring speed was set at 100 rpm. Samples of about 10 ml volume each were collected at 1, 2, 4, 6, 8, 12 and 24 h then subsequently analyzed for percentage of drug release at the respective sampling intervals. Samples were analyzed directly or after dilution with the dissolution medium at 226.5 nm using a UV spectrophotometer (Shimadzu UV-1800 240V, Japan). Triplicate observations of each type of coated pellets were used in the data analysis.

Scanning Electron Microscopy (SEM)

The surface of drug pellets and coated pellets was examined under a scanning electron microscope (Carl Zeiss EVO 40 at 20 KV, Germany). The pellets were mounted onto stubs using double sided adhesive tape.
The mounted samples were sputter coated (Poloron SC6740) under an argon atmosphere with gold palladium and examined at 15 KV accelerating voltage.

Result

Influence of wax melt coating

Hot-melt coating was used as it is more time-saving and cheaper than traditional film coating. This technology provided pellets with sustained-release characteristics. In this study, core pellets containing Venlafaxine hydrochloride were hot-melt coated with Cetosteryl alcohol at different levels i.e. 2, 4, and 6 % (wt/wt) of pellets, using centrifugal granulator. The amount of Cetosteryl alcohol in hot-melt coating layer was calculated by pellets weight gain. The drug release profile of pellets coated by the hot-melt process is illustrated in Figure 1. The results show that there was an inverse relationship between the thickness of the hot-melt coating and the rate of drug release. However, when hot-melt coating was at the 4 and 6 % level, there was no significant difference observed in dissolution. Hence, further coating at high level was not attempted. Burst release was observed as more than 90% of drug was released within 1 hour, the possible reasons being the erosion of wax layer due to vertex flow of fluid and paddle movement.
Even though hot-melt subcoating was used, it was still unable to reduce the drug release rate sufficiently. Therefore, it is recommended that the combination of melt subcoating and polymer coating may work when controlled drug release of an extremely water soluble agent is required.

Influence of Polymer

Spreading polymer dispersion on the surface of the pellets forms a plastic film coating.

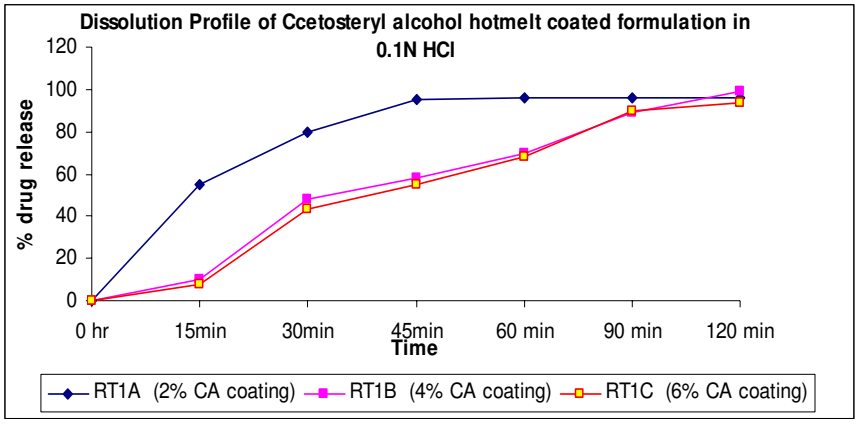

Figure 1: Influence of hot-melt coating on drug release of pellets prepared by 2% hot-melt coating weight gain; 4% hot- melt coating weight gain; 6 % hot-melt coating weight gain.

Venlafaxine HCl is extremely water soluble, and drug release from core pellets without any coating layer is fast, reaching 90% within 1 h. Consequently, a polymer coating was introduced to investigate the effect on retarding drug release. The drug release pattern from the drug-loaded pellets, prepared by using different levels of Eudragit RS 30D was faster (Figure 2) with more than 85% of the drug release within 8h. The rapid dissolution from the pellets could be due to drug migration which occurs during the polymer coating process, resulting in pores or channels producing fast drug release profile. It may also ascribed to surface erosion and formation of soluble hydrogel and wherein the drug release could happen due to both diffusion and erosion mechanism. In acidic medium 0.1 N HCl at 2 hour, 4 hour and 8 hour dissolution profiles were very high for the formulation coated with Eudragit RS 30D showed more than 10-30 % drug release at 4 hour. On the other hand, in formulation coated with Eudragit NE 30D, dissolution rates were much closer to the set limit 4 h (30-50%) and 8h (60-75%).The drug release profile for pellets prepared from Eudragit NE 30D(RT11, RT4 and RT5) at 10, 15, and 20% weight gain levels which were melt subcoated with 4 % cetosteryl alcohol is illustrated in Figure2. It can be seen that pellets with a melt subcoating level of 4% and a Eudragit NE 30D polymer coating level of 15%, achieved targeted profile. However, pellets with a 4% melt subcoating and a Eudragit NE 30D polymer coating of 10% and 20% weight gain both failed to satisfy the dissolution requirements. A fast drug release profile was observed at 10% polymer coating, whereas with 20% coating, slow dissolution profile was observed. This can be attributed to the greater thickness of polymer layer which increased the diffusional path length or, maybe, remnants sticking to the membrane. In addition, on an industrial scale, a 20% polymer coating level would be too high because of involving an increase in time required as well as increasing production costs. Consequently, the hot melt subcoating was selected to deal with the extremely water soluble drug, Venlafaxine hydrochloride.

Kinetics and mechanism of drug release

To determine the mechanism of drug release from the formulations, the data for final optimized formulation were subjected to various kinetics models using computer program;

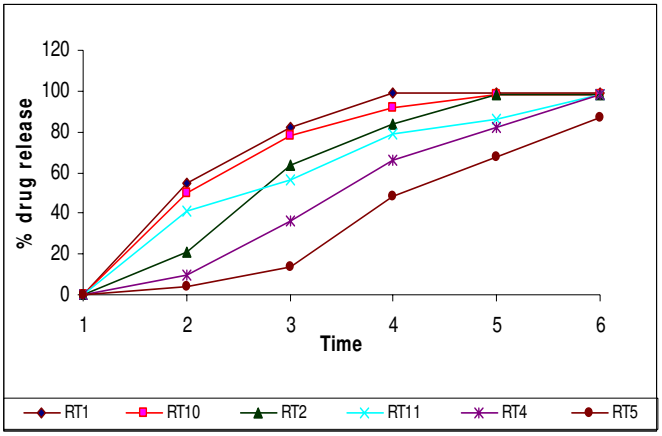

Figure 2: Dissolution profile of formulations in 900 ml 0.1 N HCl at 100 RPM in USP I apparatus.

DDSolver[14]. The dissolution data were also fitted according to the well-known exponential equation of Peppas, which is often used to describe drug release behavior from polymeric systems. The release exponent n value for spherical particles, between 0.43 and 0.85 shows anomalous type drug release involving the combination of both diffusion and erosion mechanism.

As shown in (table 5) various kinetic models were giving linear relationship. The best linearity was found in first order plot (R sq =0.9434) indicating the release of water soluble drug from porous matrices. By incorporating the first 60% of release data, mechanism of release can be indicated according to korsmeyer where n is the release exponent, an indicative of mechanism of drug release. 'n' value between 0.45 to 0.89 indicating anomalous (non-Fickian) diffusion.

Consequently, the main function of hot-melt subcoating can be attributed to three aspects: avoiding migration of the drug during polymer coating, retarding the drug release, and enhancing the effectiveness of polymer coating.

Table 2: The various mathematical models and statistics from dissolution profile

Parameter	Zero-order Model	First-order Model	Higuchi Model	Korsmeyer-Peppas Model
R_obs-pre	0.9629	0.9933	0.9885	0.9737
Rsqr	0.9166	0.9434	0.8211	0.9447
Rsqr_adj	0.9166	0.9434	0.8211	0.9263
SS	234.48	159.25	502.99	155.42
N				0.824

However, the release profile of the pellets prepared by a combination of hot melt subcoating and polymer coating satisfied the First-order and korsmeyer-peppas Model. It demonstrated that two membranes, hot melt subcoating and polymer coating, both play a significant role in prolonged drug release. Namely when the drug dissolved through the sealing

coat, it was controlled by the hot melt subcoating layer. Subsequently, polymer membrane became the main factor on controlling the drug release. If there is no hot melt subcoating layer, relying only on the polymer coating we cannot sustain drug release. Because of the presence of hydrophobic subcoating layer, dissolution medium had difficulty in wetting and crossing this layer. During dissolution, the medium should first pass through the polymer film coating layer then through the hot melt subcoating layer, and finally reach the core pellets and dissolve the drug. This result in an increased diffusion path length, since the drug solution has to diffuse through two membranes (as shown in the SEM photograph, Figure-3) before it dissolves in the surrounding membrane hence resulted in T-lag. In some cases, such as preparing pellets containing extremely water soluble drugs, if the polymer coating level is too high (such as 20 % or above), hot melt subcoating would be an alternative.

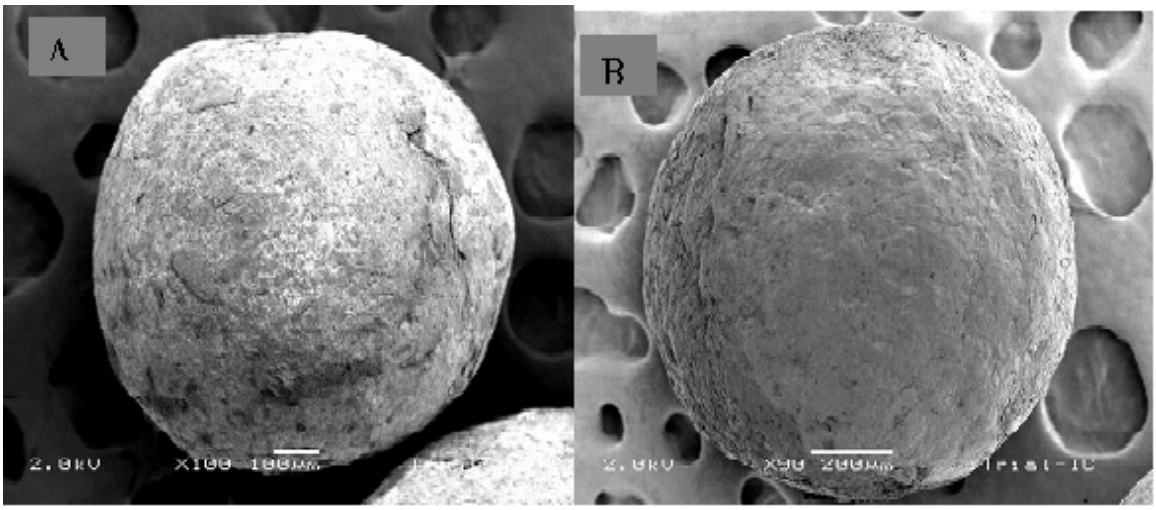

Figure: 3: SEM photograph of a pellet hot-melt subcoating level of 4% and A) polymer coating 15% weight gain B) 20% weight gain..

Conclusion

The results presented in the paper revealed that hot melt subcoating with cetosteryl alcohol enhances the effectiveness of polymer coating, avoids the migration of drug during polymer coating, and sustains drug release. It is a new way of reducing the release rate of extremely water soluble drugs. Drugs with high water solubility can be prepared as sustained-release dosage by using the hot-melt subcoating process. Formulation Trial RT 4 with a 4 % hot-melt subcoating level and a polymer coating with Eudragit® NE30D at the 15 % level met the desired drug release requirements. The release profile of the pellets prepared by this technique satisfied the first order plot (R sq =0.9434) indicating the release of water soluble drug from porous matrices. By means of this hot-melt subcoating and polymer coating combination, sustained-release pellets containing venlafaxine hydrochloride were successfully prepared.

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