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DESIGN, DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE MULTIPARTICULATE SYSTEM OF SIMVASTATIN

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ABSTRACT

The aim of the present study was to develop and evaluate a stable sustain release (SR) pellets of Simvastatin. Simvastatin requires frequent dosing due to low bioavailability and shorter half-life, so to reduce dosing frequency sustain release pellets were developed. The formulation process was carried out using Fluid Bed Processor (FBP) by Wurster technique. SR pellets were prepared using polymers Hydroxyl Propyl Methyl Cellulose E-5 LV (HPMC E-5 LV)and Eudragit NE 40D in two stages i.e. drug layering and SR coating .The study includes preformulation study, formulation, evaluation and stability studies of pellets. Excipients were found compatible and confirmed by FTIR and DSC. 2^3 factorial design was implemented by taking concentration of PVP K-30(X_1) and Eudragit NE 40 D(X_2) as independent variable and drug content and *in vitro* release as dependent variables. Optimized batch shows better *in vitro* drug release and drug content. Optimized formulation release drug upto 24 h and showed 97.83% drug release. Stability studies demonstrated no degradation of drug substance, reproducible drug patterns and no significant change in physicochemical parameters ($p < 0.05$) stored at 40°C/75% RH for 3 months.

INTRODUCTION

Simvstatin (SMV) is HMG CoA reductase inhibitor acts by decreasing cholesterol synthesis and by increasing low density lipoprotein (LDL) catabolism via increased LDL receptor activity, used in treatment of hypercholesterolaemia[1]. SMV undergoes extensive first pass metabolism due to what its absolute bioavailability is very low and frequent administration of immediate release preparations is often recommended to maintain effective blood plasma levels of SMV. In the three past decades, scientific and technological advancements have been focused on the research of sustained or controlled oral delivery systems. Some advantages of those systems are reduction in dosing frequency, reduced fluctuations in circulating drug levels, increased patient compliance, and more uniform pharmacological response[2]. Frequent administration of immediate release preparations is often recommended to maintain effective blood plasma levels of SMV, a slow and sustained release of the active ingredient is beneficial to patients to maintain sustainable levels of SMV in the blood plasma. Sustained release (SR) dosage forms are helpful when drug is absorbed throughout the GI tract. We aimed to develop sustained release capsules of SMV multiple-unit pellet system(MUPS) by using Wurster coater. As compared to conventional or immediate release dosage forms MUPS has several advantages over monolithic forms like they rapidly and homogeneously distributed in gastrointestinal tract (GIT) independent of feeding or fasting condition and hence reduce risk of local irritation and side effects[3,4]. Better plasma level profile as well as reduces inter and intra patient bioavailability [5,6].Different techniques for industrial manufacture of pellets based on melting matrices have been described with different apparatus is common to pharmaceutical industry: high shear mixers rotary processors, twin-screw extruders and fluid bed granulation [7,8,9].In this study sugar pellets were coated with active and then with polymer to retard the release using bottom spray fluid bed processor (Wurster processor). Pellets coated using this technique shows uniform size, shape and reproducible dissolution profile. In present study we used sugar pellets on which SMV is coated using bottom spray fluid bed processor and then with dispersion of HPMC E-5 LV and Eudragit NE 40 D. Combination of HPMC E-5LV and Eudragit NE 40 D can extend release of drug upto 24 h.

MATERIALS AND METHOD

SMV was kindly gifted by Ajanta pharmaceuticals Mumbai. Hydroxypropyl methylcellulose E-5 LV (HPMC E5LV), talc, Isopropyl alcohol (IPA) and polyvinyl pyrrolidone K30 (PVP K-30) was purchased from Loba chemicals, Mumbai. Eudragit® NE 40 D was obtained as gift

sample from Degussa Evonik. Sugar pellets (# 18-20, ASTM) were provided by MB Sugars, Malegaon, India. Empty hard gelatin capsules (Size 0) was supplied as a gift from Associated Capsules Pvt. Ltd., Mumbai, India. All other chemical sand reagents used in the study were of analytical grade.

DRUG LAYERING

SMV layered pellets were prepared by layering adrug-binder solution onto non-pareil sugar pellets using a fluidized bed coater (Pam Glatt, Glatt GmbH, Germany).SMV was dissolved in mixture of IPA and water (95:5) and then polyvinyl pyrrolidone (PVP 30K)and HPMC was added as a binder with continuous stirring. Then talc was added as an anti-adherent. The composition of coating solution for drug layering is shown in Table 1.Drug-binder solution was sprayed onto the pellets using the bottom spray mode. The layering conditions were: batch size, 50g, inlet temperature, 65–70 ◦C; product temperature, 33–36 ◦C; atomizing air pressure, 0.8–0.9 bar; spray rate, 0.5–1 g/min; fluidizing pressure, 0.5–0.6 bar; final drying at 40 ◦C for 30 min. The prepared pellets were then removed from the coating chamber and stored in a closed container for further experiments.

Ingredients (gm)	**D1**	**D2**	**D3**	**D4**
Sugar spheres (#18-20)	50	50	50	50
SMV	1.5	1.5	1.5	1.5
HPMC	0.35	0.40	0.45	0.50
PVP K-30	0.10	0.15	0.20	0.25
Talc	0.20	0.20	0.20	0.20
IPA/ Water	q.s	q.s	q.s	q.s

Table 1: Drug Layering On Sugar Pellets

COATING OF DRUG-LAYERED PELLETS (MODIFIED RELEASE COATING)

Eudragit®NE 40D dispersion (40%) was used as a modified release coating material to achieve a weight gain of 5, 10 and 15% (w/w) to obtain the complete multiple unit drug delivery systems. As Eudragit®NE 40D can form film without the need of plasticizer it is thus diluted with water without the incorporation of a plasticizer. Talc was added as glidant and an anti-adherant in required portion of water and stirred it for 20 min. The composition of coating solution for sustain release layering is shown in Table 2. Concentration of polymer was optimized on the basis of desired release profile. The SMV layered pellets were further

subsequently coated with an aqueous colloidal dispersion of Eudragit®NE 40D. The coating conditions were as follows: batch size, 50 g; inlet temperature, 40 ◦C; product temperature, 26–30◦C; atomizing air pressure, 0.64bar; spray rate, 0.5–1 g/min; fluidizing pressure, 0.50 bar; final drying at 30 ◦C for 30 min. The pellets were then removed from the coating chamber and stored in a closed container.

Ingredients (gm)	**S1**	**S2**	**S3**	**S4**
Drug layered pellets (gm)	50	50	50	50
Eudragit® NE40D	20	30	40	50
Talc	2	3	4	5
Purified water	20	30	40	50

Table 2: Polymeric Coating on SMV Layered Pellets (Sr Coating)

EVALUATION OF DRUG CONTAINING PELLETS

Flow properties

The micromeritic properties of pellets like bulk density, angle of repose, tapped density, Hausner's ratio were determined to check the flow properties of pellets[10,11]

Friability test

Friability of the pellets was determined by using USP friability test apparatus. Friability of the pellet formulations was determined as the percentage of weight loss after 200 revolutions of 10 g of the core pellets in a friabilator (EF 1W, Electrolab, India)[12].

Scanning electron microscopy (SEM)

Morphological properties of the pellets was examined under a scanning electron microscope (JSM 6360A, JOEL, Tokyo, Japan). The pellets were mounted onto stubs using double sided adhesive tape. The mounted samples were sputter coated under an argon atmosphere with gold palladium and examined at 20 kV accelerating voltage.

Determination of the drug content

The drug content from the pellet formulations was determined by extraction with methanol. The drug layered pellets were weighed accurately (100 mg), grounded using mortor pestle and transferred into a volumetric flask and to it 50 mL of methanol was added and the mixture was sonicated for 30 min to ensure a complete extraction. The solution was filtered through a Whattmann filter paper (125nm), diluted with appropriate amount of methanol

assayed spectrophotometrically at 238.5 nm (V-630, Jasco, Japan). Dilutions were analyzed in triplicates. The analysis was performed where Beer's Law was obeyed over the range of 2–14µg/ml. The percent drug content was calculated.

Dissolution study (in vitro drug release study)

In vitro release of SMV from pellet formulations was investigated by the USP apparatus II (paddle method – 37.0±0.5 ◦C, 50 rpm, 500 ml, Phosphate buffer pH 6.8 , n = 3). The weight of pellets used was equivalent to about 10 mg of SMV filled in capsule size 0. At certain time intervals, a 5 ml aliquot of dissolution medium was withdrawn and immediately replaced by the same volume of fresh medium to maintain sink condition. For the determination of SMV amount, the absorbance of the samples was measured at 238.5 nm by UV spectrophotometer and total amount of SMV released was calculated. The several equations which are reported in the literature to define drug release mechanism were tested with respect to the release data. To analyze the mechanism of drug release from modified release pellets, the data obtained from the drug release studies was analyzed according to the models like, zero order model, first order model[13,14], Higuchi model [15,16],Korsmeyer – Peppas model [17,18].

Stability studies

To assess the long-term stability, multiparticulate FDDS were stored at 40ºC/75% relative humidity (RH) for 3 months. After the first, second and third months, the formulations were observed for change in physical appearance, drug content and drug release profile. Stability studies were performed according to ICH guidelines [19].

RESULTS AND DISCUSSION

Fundamental design of multi-particulate floating drug delivery system

In drug layering stage HPMC and PVP K 30 was used as binder which helps better adherence of drug to the sugar pellets. In present investigation higher flexibility polymer, an aqueous colloidal polymethacrylate dispersion (Eudragit® 40 D) was chosen as a modified release membrane. When such system comes in contact with the gastro intestinal fluid, the fluid permeates trough the outer polymeric membrane, drug was released from the system for a long time.

Physical characterization

The micromeritic properties of pellets like bulk density, angle of repose, tapped density Carr's index and Hausner's ratio were evaluated to check the flow properties of pellets. The bulk density ranged from 0.628±0.009 to 0.702±0.004. The values obtained for angle of repose were 19.27±0.47 to 23.69± 0.38 which indicates good flow properties of pellets.

Hausner's ratio ranged from 1.133±0.001to1.129±0.006. The friability of the formulation was 0.15±0.09%. This indicated that the pellets were quite hard and able to withstand the mechanical stresses during the subsequent coating process.

Scanning electron microscopy (SEM)

Fig.1A reveals the surface characteristics of drug layered pellets using SEM which indicates that pellets were spherical in shape with slightly rough surface and Fig. 2 B shows Eudragit®40 D layered pellets which was smoothest.

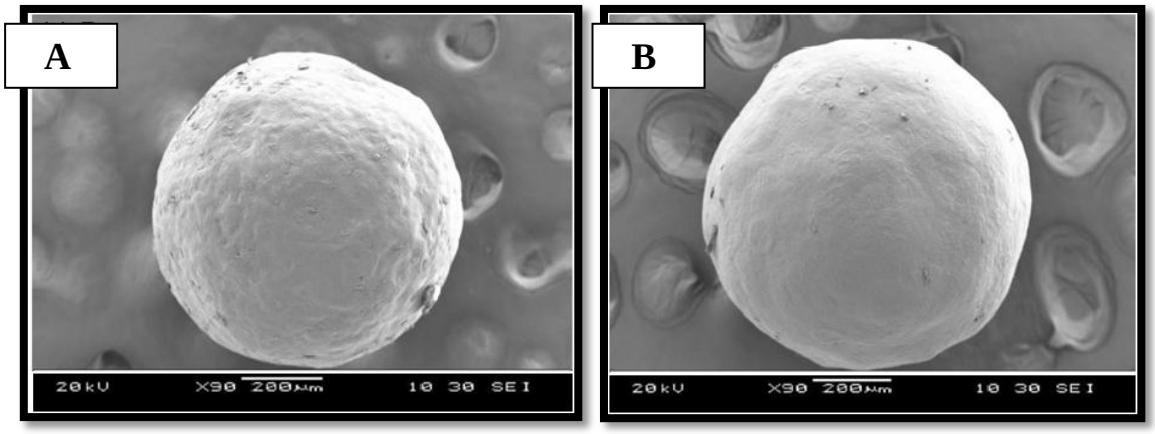

Fig. 1: Scanning electron microphotographs of (A) drug layered pellets, (B) polymeric (Eudragit®NE 40 D) layered pellets.

Determination of the drug content

SMV content in the coated pellets was determined by using UV spectrophotometer. The results showed that the content in any preparation was in a range of 97.4% and 101.7%.The results indicated that the multilayering also could produce the pellets with good reproducibility of drug content.

Dissolution study (in vitro drug release study)

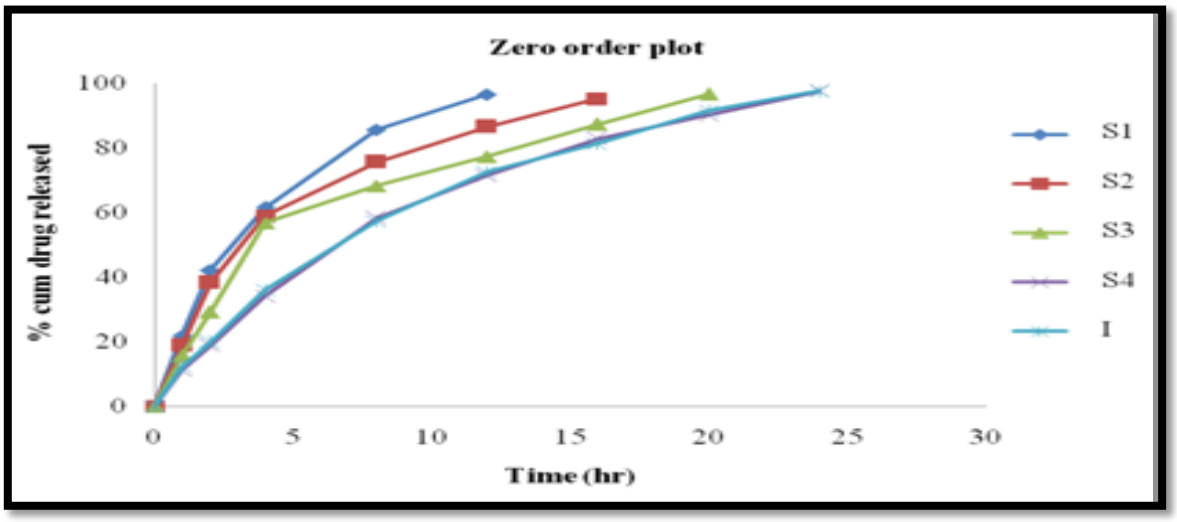

Fig. 2: In vitro drug release SMV from Eudragit® coated pellets.

The in vitro release pattern of the SMV coated pellets is shown in Fig. 2. The release behavior of batches PB1 to PB4 changed due to the variation in the concentration of HPMC and Eudragit® NE 40D in modified release layer. As the concentration of Eudragit® NE 40D was increased the drug release was retarded. Eudragit® NE40D was one of low permeability, pH independent swelling coating polymers[3].The higher membrane thickness retarded water penetration, resulting in decreasing drug release[19].In vitro release experiments were evaluated in order to investigate the release of drug from the coated pellets. To determine the mechanism and kinetics of drug release, the data was analyzed by various models like zero order model, first order, Higuchi model, Korsmeyer–Peppas model. Table 3 illustrates the regression coefficients obtained from various mathematical analyses. The dissolution profiles of all coated pellets indicated that the drug release follows either zero order or Higuchi's model. The initial fast release could be due to both dissolution and diffusion from the surface and outer zone of the pellets. As the drug in the outer zone was depleted, the drug particles in the inner area diffused through the coated film at slower rate.

Formulation	Zero order	First order	Higuchi Model	Korsmeyer-peppas
PB1	0.9913	0.9254	0.9765	0.9543
PB2	0.9945	0.9321	0.9685	0.9487
PB3	0.9878	0.9367	0.9779	0.9572
PB4	0.9975	0.9389	0.9793	0.9684

Table 3: Regression Coefficients of Various Mathematical Models

Stability studies

In the design of any dosage form stability of the product must be the basis for acceptance and rejection. During stability studies the product is exposed to accelerated conditions of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature for short period of time. The stability data of the coated pellets of SMV is shown in Table 4. No physical changes were observed during storage. The results obtained in the stability test showed that the drug content and in vitro drug release profile from the system stored at a temperature of 40 ◦C and a relative humidity of 75% was unchanged during a 3-month period of accelerated storage conditions. Drug content and in vitro drug release profile after 1, 2 and 3 months showed no significant differences ($p > 0.05$). This indicated that the pellet formulation was stable.

Time/ months	Appearance	Drug Content (%)	*In vitro* drug release(%)
0	White	99.15 ± 1.38	97.77 ± 2.94
1	White	98.67 ± 2.92	97.58 ± 3.04
2	White	97.58 ± 2.73	97.49 ± 3.13
3	White	97.07 ± 1.16	97.36 ± 2.98

Table 4: Stability Study Results for Coated Pellets.

CONCLUSION

The SMV sustained release pellets were successful prepared. The formulation of the uncoated pellets included HPMC, Binder PVP K30 and SMV. The uncoated pellets achieved good sphericity, low friability, narrow particle size distribution and smooth surface. The coating polymer Eudragit NE 40D and coating weight gain 8.5% could prepare the desired SMV sustained-release pellets. As concentration of Eudragit increases the release of SMV was retarded. From this study we come to know that combination of HPMC and Eudragit polymer can be used to achieve development of SR systems which can give drug release up to 24 h. In present investigation 97.54% of SMV was released in 24h.

REFERENCES

1. Todd P. A, Goa K.L. Simvastatin. A review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. Drugs Oct 1990, 40(4): 583-607.
2. Welling, P.G, Dobrinska, M.R. Dosing considerations and bioavailability assessment of controlled drug delivery systems. Controlled drug delivery, fundamentals and application. In: Robinson, J.R., Lee, V.H.L. (Eds.), Drugs and the Pharmaceutical Sciences, volume 29, 2nd edition. 1987; Marcel Dekker, New York.
3. Lin L, Jin S. Preparation and evaluation of sustained-release diltiazem hydrochloride pellets. Asian J. Pharm. 2013; 244-251.
4. Shajahan A, Chandewar A. V, Jaiswal S.B, A flexible technology for modified-release drugs: Multiple-unit pellet system (MUPS), J. Controlled Rel. 2009; 147, 2-16.
5. Decheshe J. P, Delattre L. A new enteric tablet of acetylsalicylic acid: biopharmaceutical aspects, Int. J. Pharm. 1996; (34) 257–262.
6. F. Stanislaus, H.J. Huber, Different drug delivery systems in bioavailability studies, in: B.W. Müller (Ed.), Controlled Drug Release, 1987; 56–68.

7. Thomsen L.J. Prolonged release matrix pellets prepared by melt pelletization IV. Drug content, drug particle size, and binder composition, Pharm. Technology. Europe 6 1994; 19–24.
8. L.J. Thomsen, T. Schaefer, J.M. Sonnergaard, H.G. Kristensen, Prolonged release matrix pellets prepared by melt pelletization – I. Process variables, Drug Dev. Ind. Pharm.1993; 1867–1887.
9. Frake P, Greenhalgh D, Grierson SM, et al. Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy. Int J Pharm 997; 151: 75-80
10. Ghebre-Sellassie I, Pellets: a general overview, in: I. Ghebre-Sellassie (Ed.), Pharmaceutical Pelletization Technology, Marcel Dekker Inc., New York, 1989.
11. Amrutkar P. P, Chaudhari P. D, Patil S. B. Design and in vitro evaluation of multiparticulate floating drug delivery system of SMV. Colloids and Surfaces B: Biointerfaces 89 (2012) 182– 187.
12. Kim S. M, Kim J. S, H wang S. J. The effect of sodium alginate on physical and dissolution properties of Surelease matrix pellets prepared by a novel pelletizer, Chem. Pharm. Bull. 55(11)(2007)1631–1634.
13. Costa P, Lobo M.S. Modeling and comparison of dissolution profiles, Eur. J. Pharm. Sci. 13 (2001) 123–133.
14. Ritger P. L, Peppas, N.A. A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices, J. Controlled Release 5(1987) 37–42.
15. Lopes C. M, Lobo J. M. S, Pinto J. F, Costa P. Compressed mini-tablets as a biphasic delivery system, Int. J. Pharm. 323 (2006) 93–100.
16. Lee A. J, King J. R, Hibberd S. Mathematical modeling of the release of drug from a porous, non-swelling transdermal drug delivery devices, Math. Med. Biol. 15(2) (1998) 135–163.
17. Korsmeyer R. W, Gurny R, Doelkar E, Buri P, Peppas N. A. Mechanism of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983)25–35.
18. Peppas N. A. Analysis of Fickian and non-Fickian drug release from polymers, Pharm. Act a Helv. 60 (1985) 110–121.
19. Ichigawa M, Watanabe S, Miyake Y. A new multiple-unit oral floating dosage system. I. Preparation and in vitro evaluation of floating and sustained-release characteristics, J. Pharm. Sci. 80 (1991) 1062–1066.