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Design and characterization of modified release pellets of metoprolol tartarate using hot-melt coating excipients

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ABSTRACT

Multi-unit dosage forms are becoming popular for providing sustain release of drugs in the gastrointestinal (GI) tract as they diminish chances of dose dumping. They usually consist of a drug entrapped in a sustaining matrix or of a drug coated reservoir with a low permeability coating material film. Pellets are one of the multi-unit delivery system and are prepared to obtain sustained drug delivery, to improve bioavailability or stability and to target drug to specific sites. Metoprolol tartarate was used as tracer and transformed into pellets by drug layering technique. Lipids are the materials which can be used to coat the drug in order to control the release. Application of fine layer of coating material in molten state over the substrate is known as hot-melt coating technique. Bees wax and cetyl alcohol are hydrophobic excipients used as a rate-controlling membrane to modulate the drug release from dosage forms. Coating conditions (temperature, speed of pan rotation, air pressure, etc.) were investigated for the production of modified release pellets and dissolution kinetic curves were discussed. The optimized conditions confirm previous work, underscoring the considerable importance of the temperature of molten coating materials and the air pressures. Results reveal that, surface adhesion of coating excipients over pellets was controlled and consistent. The coating was uniform under controlled conditions and drug release from coated pellets was directly proportional to amount of coating excipients. Formulations stored for stability study were found to be stable during course of study as per ICH guidelines.

Keywords: Bees wax, Cetyl alcohol, Drug layering technique, Hot-melt coating, Metoprolol tartarate.

INTRODUCTION

The use of coating pan processing in the development and production of solid dosage forms is on the increase. Coating pans are traditionally used for coating of beads, capsules, granules, pellets, tablets and spherules using pan pour or spray techniques. Generally speaking, the coating material is dissolved in a solvent (water or organic or mixture) prior to coating [1-3]. During and after coating the solvent must be evaporated. The use of solvents nowadays is under constraint due to the problems of trace levels [4], while recovering a solvent often proves expensive. Organic solvents show hazardous effects on operators as well as environment [5, 6]. Due to its long evaporation time water, microbial contamination of dosage form and hydrolysis of drug could be the problem. In order to avoid such problems and to reduce the production costs, it is appealing to use a meltable product like wax or their derivative as coating materials.

However, very little literature was published by the few authors on this technique in the pharmaceutical literature. An outstanding review of the process conditions and equipment for hot-melt coating has been published by Jones and Percel [7]. Wax formulations for coating drug-loaded sugar beads have been investigated by Bhagwatwar and Bodmeier [8], while Achanta et al. [9] have written a general overview of the development of pharmaceutical coating technologies, including hot-melt coating methods.

The present study was aim to confirm suitability of bees wax and cetyl alcohol as hot-melt coating excipients to design modified release pellets of metoprolol tartarate. Hot-melt coating requires a 12 inch diameter conventional coating pan with four radially arranged baffles without spray system. The most fascinating part of this research is the study of the influence of process variables on the characteristics of coated pellets through a modified central composite design.

MATERIALS AND METHODS

Materials: Metoprolol tartarate was kind gift sample from Lincoln Pharma. Ltd., Ahmedabad, India. Microcrystalline cellulose (Avicel PH 101), non-pareil seeds and polyvinyl pyrrolidone K-30 (PVP K-30), Diethyl phthalate (DEP) were procured from Themis Laboratories, Mumbai, India. Bees wax, cetyl alcohol were purchased from S.D. Fine Chemicals, Mumbai, India. All other chemicals were of analytical and laboratory grade.

Preparation of drug loaded pellets: Non-pareil seeds (0.5 kg) were placed in the pre-warmed chamber of a coating pan (12 inch diameter) with four radially arranged baffles which operated at the speed of 30 rpm. Binder solution was prepared by dissolving polyvinyl pyrrolidone in isopropyl alcohol (5% w/v). Spray application of drug-binder solution (1 ml/min), along with simultaneous application of drug and talcum powder (10-20 g/min) on non pareil seeds were carried out. After a sufficient quantity of powder was added to build the pellets to the desired size, spraying of the binder solution was terminated. The pellets were dried in the chamber; the blower air velocity was at 7 m/sec. The dried pellets were screened and the 16-20 mesh fractions collected. Pellets were kept in a hot air oven and dried at 45-50 ^{o}C for 2 hr.[10]

Hot-melt coating of drug loaded pellets: These drug loaded pellets were coated with different concentrations of drug release controlling materials namely bees wax or cetyl alcohol (5, 8 and 10%) with ethyl cellulose (10% w/w of wax) and DEP (plasticizer) using hot melt coating technique by loading of melted wax over pre-warmed drug loaded pellets (45-50^{o}C). After the desired weight of film was deposited, cooling and congealing of wax coated pellets were carried out (congealing time 12 hrs).[11] The coating composition are given in Table 1.

Table 1: Formulation of hot-melt coating composition

Formulation	Coating composition		
	Bees wax (% w/w)[a]	Cetyl alcohol (%w/w)[a]	Ethyl cellulose (% w/w)[b]
M1	10	--	--
M2	--	10	--
M3	5	--	10
M4	8	--	10
M5	10	--	10
M6	--	5	10
M7	--	8	10
M8	--	10	10

Where, [a] indicates % w/w of wax of pellet amount and [b] indicates % w/w of ethyl cellulose of coating composition.

Evaluations of metoprolol tartarate pellets

Pellet size determination: Size determination was carried out using sieve analysis method. Approximately 200 g of pellets was placed into a sieve shaker equipped with 8-, 12-, 16-, 18-, 20-, 30- and 40-mesh US standard sieves (Acmas Tachnocracy, India) and shaken for 20 min. Each weight fraction was recorded. The mean size for coated as well as uncoated pellets was determined. Shape and surface morphology view of the gold-treated pellets were photographed using a scanning electron microscope (Jeol Model JSM-35CF, Japan) [12].

Angle of Repose: Accurately weighed 50 g of pellets were poured gently through glass funnel on the graph paper. The height of pile and diameter were noted and angle of repose for uncoated and coated pellets were calculated.

Hardness and friability: The hardness of uncoated and hot-melt coated pellets was examined by Veego digital dial type hardness tester (Veego Scientific®, India). For the friability study, 10.0 g pre-weighed pellets, collected on sieve having 0.85 mm aperture with 25 glass beads of 3 mm diameter were placed in Roche's friabilator (Veego Scientific®, India) for 100 revolutions at 25 r/min speed. The mass of pellets placed on sieve with 0.85 mm aperture. The smaller particles were allowed to pass through the sieve and pellets were reweighed. The friability was determined as percentage loss of mass of pellets after test was recorded [13-15].

Determination of metoprolol tartarate content: An accurately weighed portion of pellets, equivalent to about 100 mg of metoprolol tartarate, was dissolved in absolute methanol, filtered and adjusted to the desired concentration with 0.1N HCl. The UV absorbance of the solution was determined at 276 nm. The percent drug content was calculated [16].

Dissolution of metoprolol tartarate pellets: An automated dissolution setup comprised a dissolution apparatus, a six-channel peristaltic pump, a UV/visible spectrophotometer equipped with six 1-cm quartz flow cells. For both uncoated and coated pellets the dissolution test was carried out. Release of metoprolol tartarate from coated pellets was carried in 900 ml of 0.1 N hydrochloric acid using dissolution test apparatus 2 USP XXIV (Electrolab®, India). A six station dissolution test apparatus was used. One capsule containing 100 mg of metoprolol tartarate coated pellets, a speed 100 r/min and a temperature of 37±0.5°C were employed in each test; samples were withdrawn through a filter at different time intervals, suitably diluted and assayed for metoprolol tartarate at 276 nm using double beam UV/visible spectrophotometer (Schimadzu® UV-1601, Japan). Drug release studies were conducted using sample size six [16].

Stability studies: Optimized formulation was kept in the humidity chamber (Lab Top®, India) maintained at 40°C and 75% relative humidity for 3 month. At the end of studies, the formulation was subjected to drug content, hardness, friability and *in vitro* dissolution studies. For the comparison of release profiles of initial and aged samples, the difference factor (f_1) and similarity factor (f_2) were calculated [17], [18].

RESULTS AND DISCUSSION

Preparation of metoprolol tartarate pellets: Hot-melt coating is faster and cheaper than the conventional coating techniques where evaporation and/or recovery of solvent can be expensive, tedious and time consuming. Technique is safe for the operators as well as environment. The modified pan coater is recommended for this purpose because of its ability to operate at the production temperature close to the congealing temperature of the molten mass, which is essential for producing a continuous coating on the particles. In addition, this coating technique enhances stability and provides taste masking and sustained release characteristics to the pellets. In this study, pellets containing metoprolol tartarate were prepared by drug layering technique. Both core drug pellets and hot-melt coated pellets were successfully prepared.

As shown in Fig. 3 the release of metoprolol tartarate lowered when the percent of wax coating was increased (5, 8 and 10%). Thus prolongation of release profile can be directly attributed to the amount of wax coating applied. Burst release was observed as more than 80% release of drug released within 2 hr, the reasons might be the erosion of wax layer due to vertex flow of fluid and paddle movement due to which immediate release was observed. The wax coating alone was not sufficient in retarding the release of drugs. But our aim was to produce sustained release product, therefore hydrophobic material ethyl cellulose was used in association with wax to coat the pellets. *In vitro* dissolution studies on cetyl alcohol and bees wax coating (5, 8 and 10%) along with 10% ethyl cellulose of wax.

Evaluation of metoprolol tartarate pellets

Physical characteristics: The average size of the uncoated pellets was found to be 845 µ. Sieve analysis revealed that the coated pellet size was found in the range of 852-913 µ as shown in [Table 2]. The uncoated pellet as shown in [Fig.1] appeared to possess spherical shape and with slightly rough surface. Fig. 2 shows the shape and surface of the hot-melt coated pellets of metoprolol tartarate. It could be seen that the coated pellets were spherical and with smooth surface due to uniform coating pattern. However, the surface roughness of uncoated pellets was diminished with the application of coating wax [Fig. 2]. The pellets have good flow property with low friability and sufficient crushing strength [Table 2].

Fig. 1: SEM of uncoated pellets of metoprolol tartarate (30X)

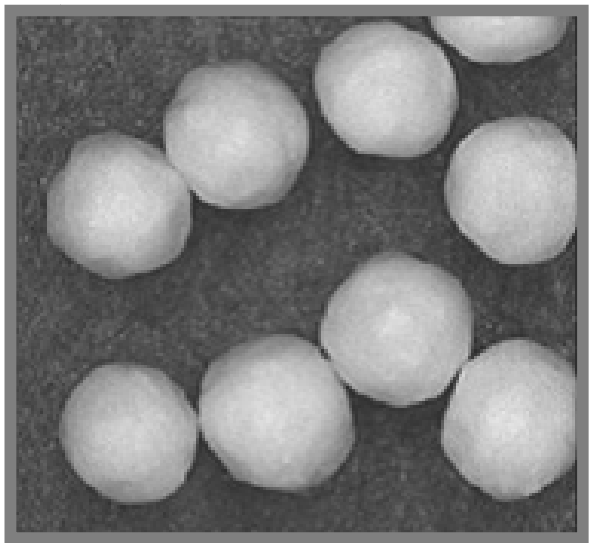

Fig. 2: SEM of hot-melt coated pellets of metoprolol tartarate (30X)

Table 2: Mean particle size, hardness, friability and drug content in uncoated and HMC pellets

Formulation	Mean pellet Size (μ)	Angle of Repose[a] (°)	Hardness[a] (kg/cm^2)	Friability[a] (%)	Drug Content[a] (%)
M1	854	24.15 ± 0.012	2.40 ± 0.10	0.22 ± 0.002	99.84 ± 1.123
M2	852	23.04 ± 0.021	2.35 ± 0.15	0.23 ± 0.004	99.79 ± 2.036
M3	873	21.42 ± 0.005	2.65 ± 0.25	0.21 ± 0.003	100.46 ± 2.226
M4	892	20.78 ± 0.030	2.80 ± 0.20	0.18 ± 0.005	101.05 ± 1.013
M5	910	18.44 ± 0.019	2.95 ± 0.05	0.17 ± 0.004	100.11 ± 3.022
M6	876	20.27 ± 0.023	2.45 ± 0.15	0.22 ± 0.001	98.83 ± 0.170
M7	895	18.97 ± 0.017	2.55 ± 0.15	0.20 ± 0.003	99.39 ± 3.545
M8	913	17.59 ± 0.009	2.75 ± 0.10	0.19 ± 0.002	98.95 ± 2.173
M0	845	26.75 ± 0.027	1.95 ± 0.20	0.42 ± 0.006	100.88 ± 2.346
M5S	915	17.98 ± 0.015	2.90 ± 0.15	0.16 ± 0.003	98.64 ± 2.226
M8S	913	17.54 ± 0.016	2.70 ± 0.15	0.18 ± 0.003	98.93 ± 3.263

Where, [a] indicates values are (Mean ±SD) when sample size is in triplicate, M0 indicates uncoated pellets , M5S & M8S indicates formulations M5 and M8 stored for stability study as per ICH guidelines for 3 months.

Determination of metoprolol tartarate contents: Metoprolol tartarate contents in uncoated and coated pellets were determined by using UV/visible spectrophotometer. [Table 2] shows the content in any preparation was in a range of 98.83% and 101.46%. The results implied that present pelletization could produce the pellets with good reproducibility of drug content. The drug content in the pellets was found to be within limit as per United State Pharmacopoeia (USP).

Dissolution of metoprolol tartarate pellets: The release of metoprolol tartarate from the hot-melt coated pellets coated with 10% of bees wax or cetyl alcohol can retard dug release but not more than 2 hrs.

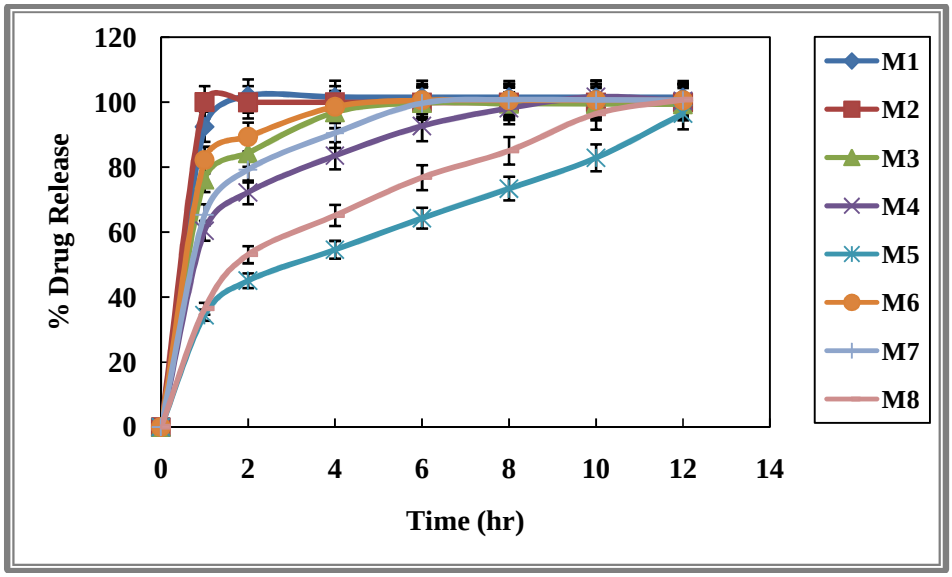

Figure 3: *In vitro* dissolution study of hot-melt coated formulations

This was due to the reason that during dissolution study, wax layer was slightly eroded due to movement of paddle as well as dissolution medium (vertex formation) and therefore immediate release of drug was observed. Therefore, ethyl cellulose was used in combination with bees wax or cetyl alcohol to provide the strength to wax layer on the surface of pellets. Using 10% ethyl cellulose of coating level was used along with wax to coat the pellets for design of sustained release product. Formulation M5 and M8 were showing release profile similar to targeted release profile and hence were selected as optimized formulation. Formulation M5 was showing difference factor (f_1) and similarity factor (f_2) values 7.11 and 62.34 respectively. Whereas formulation M8 was showing difference factor (f_1) and similarity factor (f_2) values 6.28 and 67.41 respectively. Hence, M5 and M8 were stored for stability testing as per ICH guideline.

Table 3: Kinetic data analysis

Formulation	Zero order Model		First order Model		Higuchi model	Korsmeyer Peppa's model		Hixon- Crowell model
	K_0	R^2	K	R^2	R^2	R^2	n	R^2
M1	4.359	0.5354	0.188	0.5057	0.7364[b]	0.3992	0.742	0.5169
M2	4.007	0.4958	0.184	0.4964	0.6989[b]	0.3878	0.716	0.4961
M3	5.161	0.6588	0.197	0.5385	0.8380[b]	0.4219	0.828	0.5857
M4	6.187	0.7945	0.211	0.5838	0.9303[b]	0.4454	0.905	0.6731
M5	6.561	0.9441	0.229	0.6733	0.9924[b]	0.4621	0.982	0.8084
M6	4.939	0.6236	0.195	0.5278	0.8098[b]	0.4145	0.798	0.5647
M7	5.837	0.7371	0.206	0.5646	0.8947[b]	0.4414	0.890	0.6366
M8	7.186	0.9702	0.231	0.6503	0.9881[b]	0.4739	0.967	0.7775

Where, [b] indicates best fitted kinetic model for the formulation.

The kinetic analysis of data for dissolution profiles of all coated pellets prepared under these experimental conditions indicated that the drug release follows Higuchi 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. In an attempt to describe the kinetics of drug release, several mathematical models were used to express the drug release [19]. Drug release from the sustained release pellets occurred by diffusion, which was reflect from Higuchi model. [Table 3] illustrates the coefficients of determination obtained from various mathematical analyses. The 'n' value for all the formulations were lies between 0.5-1.0, the drug release mechanism can be concluded as non-Fickian diffusion mechanism.

Stability studies: In view of the potential utility of the formulations, stability studies were carried out at 40°C and 75% RH for 3 month (for accelerated testing) to assess their long-term stability. Analysis of the dissolution data [Fig. 4], after storage for 3 month, showed no significant change in the release pattern indicating that the two dissolution profiles were similar with similarity factor (f_2 >50). The other parameters like angle of repose, mean pellet size, drug content, hardness and friability evaluated were significantly similar with initial values.

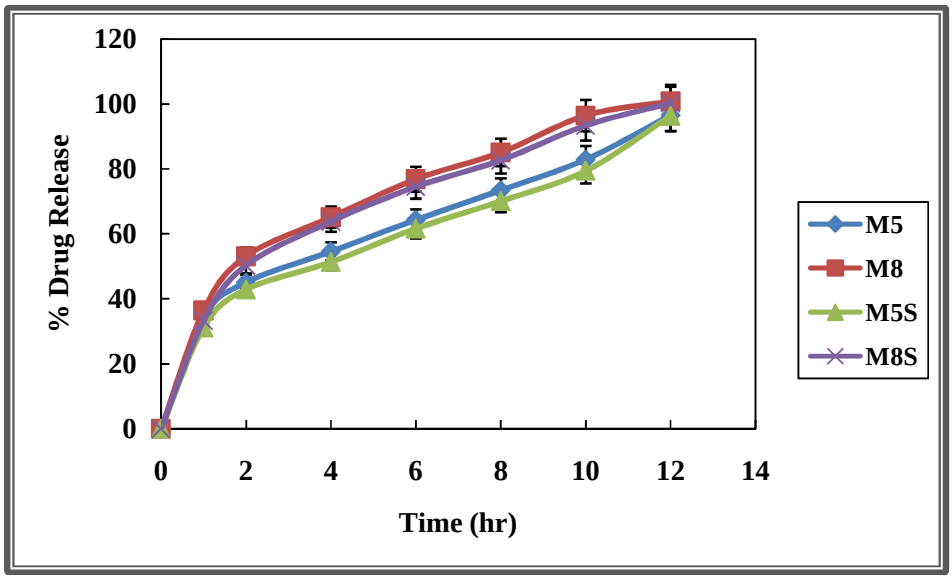

Fig. 4: Stability study of optimized formulations

CONCLUSION

Metoprolol tartarate pellets were successfully prepared by drug layering pelletization technique. The pellets prepared by this mean were spherical in shape and had relatively smooth surface. A narrow particle size distribution was achieved. The pellets were coated with bees wax or cetyl alcohol in association with ethyl cellulose using hot-melt coating technique in a modified conventional pan coater and proven to be successful. Hot-melt coating technique presents an easy, economic, rapid and simple choice compared to conventional coating methods where solvent evaporation and recovery could become very expensive and time consuming.

The results revealed that hot melt coating with cetyl alcohol or beeswax alone, unable to retard the release of the drug. This was due to reason that during dissolution study, wax layer was slightly eroded due to movement of paddle as well as dissolution medium (vertex formation) and therefore immediate release of drug was observed. Therefore, ethyl cellulose was used in combination with bees wax and cetyl alcohol to provide the strength to wax layer on the surface of pellets. Formulation M5 and M8 were selected as optimized formulation. Optimized formulations stored according to ICH guidelines were found to be stable. Hot-melt coating technique was proved to be economic way of manufacturing sustained release formulation. Ethyl cellulose (10%) with wax coating pellets produced more sustained release product. From kinetic analysis drug release from the hot-melt coated pellets was primarily controlled by drug diffusion through the intact coating.

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