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Preparation of Diltiazem Hydrochloride Extended Release Pellets by Novel Hot-Melt Extrusion and Spheronization Process

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Abstract: Membrane coated drug pellets is a common way of preparing controlled release drug multiparticulates. A good alternative to it is preparation of matrix pellets by hot melt extrusion-spheronization, wherein the drug release is modulated by use of hydrophobic low melting waxes. The present study is an attempt towards preparation of hot melt matrix pellets of dilitiazem hydrochloride, using melt extrusion-spheronization methodology, which demonstrates extended drug release profile and complies with the dissolution pattern stated in USP, without the need for application of a polymeric membrane.

Key words: Hot melt extrusion-spheronisation, diltiazem hydrochloride, extended release pellets, Compritol 888ATO, stearic acid.

Introduction

The aim of preparation of diltiazem hydrochloride extended release pellets is to achieve a predictable and reproducible drug release rate over an extended period of time to allow for once daily administration. Extended-release delivery systems allow reduced dosing frequency and provide constant drug levels in the blood, thus increasing patient compliance and decreasing adverse drug events.[1] Pellets are frequently used in controlled-release systems because they disperse freely in the gastrointestinal tract, offer controlled absorption with resultant reduction in peak-to-trough ratios, the absorption of drug is unaffected by feeding state, pose minimal potential for dose dumping and provide greater flexibility in product design, modification and development of combination dosage forms.[2] Further, they can be tailored to target release of drug to specific areas within the gastrointestinal tract. Traditionally, pellets are prepared by drug layering (as powder, solution or suspension) on nonpareil seeds in a conventional coating pan, tangential fluid bed processor or Wurster coater and by extrusion-spheronization. The drug release from pellets prepared by these methods is controlled by the aqueous or non-aqueous polymer coating. One such patented technology for the production of controlled release diltiazem hydrochloride pellets belongs to Andrx corporation.[3] The process of application of rate-controlling polymeric membrane to drug pellets requires multiple steps and reproducibility is thus a great issue. To overcome these problems and avoid coating of drug pellets, a better alternate would be preparing matrix drug pellets in a single step. One of the ways of achieving such a product is melt extrusion-spheronisation. One of the approaches in the production of controlled release pellets of water soluble drug like diltiazem hydrochloride is hot melt extrusion and spheronization.[4]

Materials and Methods

Materials

Diltiazem hydrochloride, Compitrol 888ATO (glyceryl behenate) from Gattefosse S.A, stearic acid (Godrej) and microcrystalline cellulose (FMC, Newark, Delaware).

Drug–excipient Interaction Studies

The possibility of drug–excipient interaction was investigated by differential scanning calorimetry. The DSC thermograms of pure drug, individual excipients and drug–excipient mixtures were recorded. The samples were separately sealed in aluminium cells and set in Mettler Toledo thermal analyzer. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10^0C/min over a temperature range of 30–300 ^{0}C. Alumina was employed as the reference standard.

Preparation of Controlled Release Hot Melt Extruded-Spheronized Drug Pellets

Several experiments were carried out for pellet formulation by melt-processing and consisted of use of meltable excipients such as fatty acid (stearic acid), fatty acid ester (Compitrol 888ATO) and polyethylene glycol 6000 and admixture of molten waxes with diltiazem hydrochloride. The experiments involved use of lone rate-controlling ingredient and their combination(s). Microcrystalline cellulose was used as the spheronizing aid.[5] The formulae used for different experiments are mentioned in table 1. The functional ingredients and drug were sifted through a 40-mesh screen and the powder formulation was blended for 10 min at 100 rpm in a high-shear granulator (Tapasya). The dry powder blend was extruded using a Fuji Paudal MG-55 vertical, single-screw extruder. The conveying zone temperature was 70°C to 80°C and die temperature of the extruder was maintained between 110°C to 120°C.[6] The formulation blend was fed into the hopper only after the extruder zones and die had equilibrated to the set temperatures required for melting of waxes. The hot melt extrudates exiting from the die of diameter 1.22 ± 0.03 mm was immediately fed into spheronizer, the temperature of which was previously maintained at 80°C, and subjected to spheronization for 5 minutes at 800 rpm.[7-9] The pellets so formed were allowed to cool/congeal to ambient temperature. Pellets of particle size 810 to 1400 microns were collected and analysed for drug release. Table 1 presents the compositions of different matrix pellet formulations prepared by hot-melt extrusion-spheronization.

In vitro Dissolution of Controlled-release Matrix Pellets

The pellets of formulations F1, F2, F3 and F4 were subjected to dissolution studies as per USP-32 test 5 for "Diltiazerm Hydrochloride Extended Release Capsules" for 12 hours dosing.[10] Dissolution test conditions comprised of use of USP dissolution apparatus 2 (paddle) operated at speed 50 RPM for 8 hours. Dissolution media was 900 ml of 0.05 M phosphate buffer pH 7.2 at 37±0.5◦C. For each formulation, 340 mg of weighed amount of pellets (equivalent to 90 mg diltiazem hydrochloride) was subjected to dissolution studies. Aliquots (10 ml) were withdrawn at 1, 3 and 8 hour time intervals, filtered and diluted with dissolution fluid to obtain a solution of concentration 10 mcg/ml. Absorbance of diluted aliquots was determined spectrometrically at λmax 237 nm.

Microscopy of Hot Melt Processed Drug Pellets

Scanning electron microscopy of HME pellets of diltiazem hydrochloride was performed to assess the surface morphology of melt-processed multiparticulates.

TABLE 1: Composition of different formulations

Ingredients (mg/cap)	F1	F2	F3	F4
Diltiazem hydrochloride	90	90	90	90
Microcrystalline cellulose	45	45	45	45
Compitrol 888 ATO	-	200	160	120
PEG 20000	10	10	10	10
Stearic acid	200	-	40	80
Total	340	340	340	340

TABLE 2: In vitro Release Profile Diltiazem Hydrochloride from Different Hot-melt Processed Pellet Formulations

Time (hours)	% Drug release of formulation				Acceptance criteria USP Test 5
	F1	F2	F3	F4	
1	60.23	10.67	10.23	10.50	Not more than 15%
3	98.23	45.64	50.67	59.07	Between 45 &70
8	100.01	62.97	68.23	88.07	NLT80%

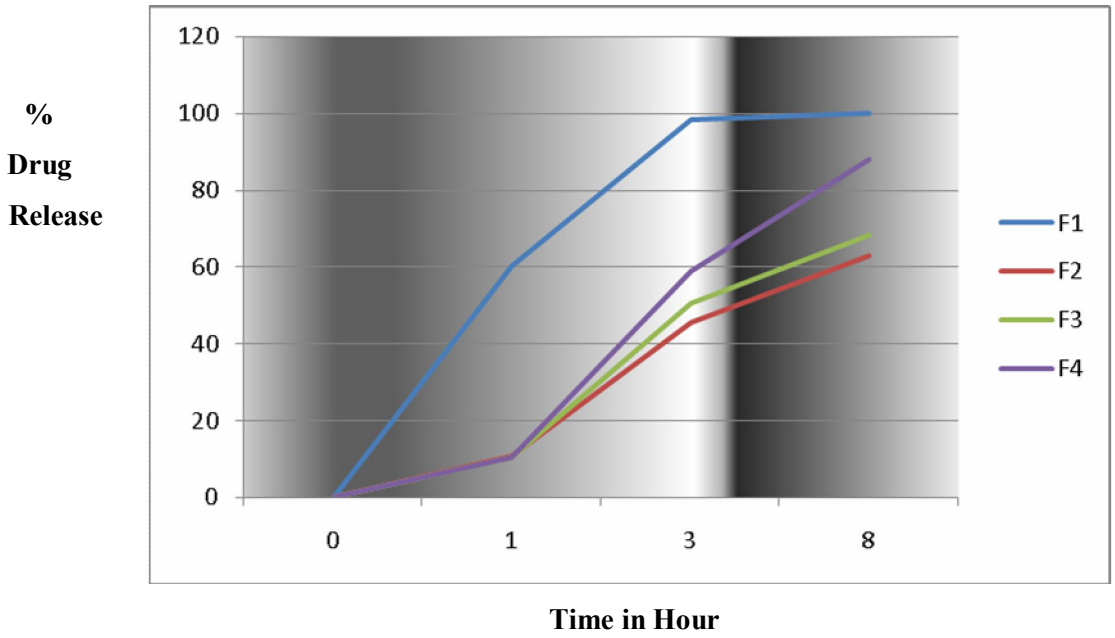

FIGURE 1. In vitro dissolution profile of diltiazem hydrochloride from hot melt extruded pellets

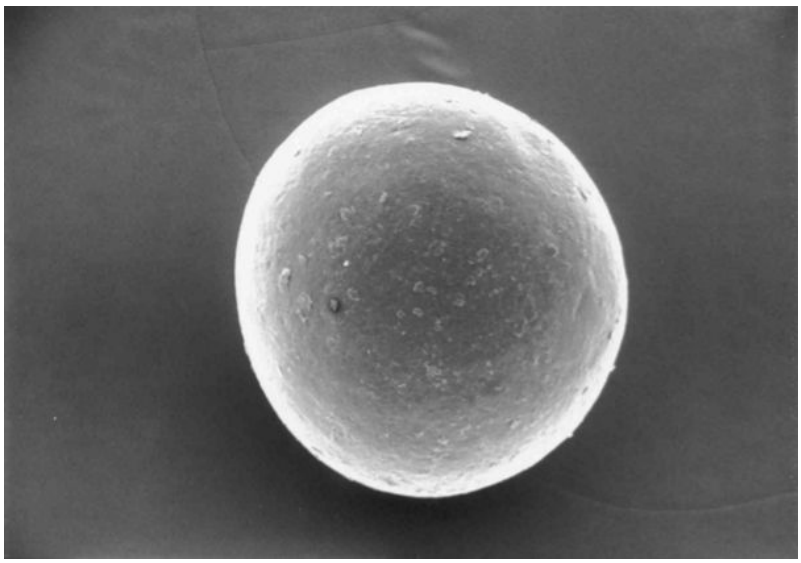

FIGURE 2. SEM of diltiazem hydrochloride hot-melt processed pellets (magnification 200 X)

Results and Discussion

In the present study, thermal process (hot melt extrusion-spheronization) was used to prepare controlled release pellets of diltiazem hydrochloride. Pellet formulations containing various ratios of drug-to-lipid were prepared to achieve the desired release profile. Each hydrophobic lipid had the potential to extend drug release from hot melt processed pellets of diltiazem hydrochloride. Compitrol 888ATO acts as release-retardant, stearic acid functions as release-modifier whereas polyethylene glycol 20000 facilitates thermal processing by lowering the glass transition temperature of the drug-lipid, lowers congealing temperature and provides viscoplastic nature to extruded pellets which is essential for spheronization. Furthermore, polyethylene glycol also functions as release modifier. Microcrystalline cellulose acts as anti-tack agent and spheronizing aid.

Formulations F1, F2, F3 and F4 contained similar concentration of PEG 20000 and microcrystalline cellulose.

Results of drug-excipient compatibility studies revealed that there is no untoward interaction between drug and the excipients chosen for the study.

Dissolution studies conducted as per USP methodology revealed that formulation F1 that contained stearic acid as the release-retardant, did not sustain the dissolution as desired and yielded faster drug release (table 2). This was because of saponification of stearic acid in dissolution media (alkaline buffer pH 7.2) resulting in rapid erosion and dissolution of microspheres. Formulation F2 contained Compitrol 888ATO as the release controlling fat. In vitro dissolution of these pellets demonstrated remarkably retarded release profile of drug which was more than that desired as per the USP monograph. In order to compensate rapid release effect of stearic acid and greater retarding effect of Compritol 888 ATO, combination of these two lipids was done to arrive at formulations F3 and F4. In vitro dissolution results demonstrated that the formulation in which ratio of Compritol 888ATO to stearic acid was 3:2 (formulation F4) provided release profile that complied with USP monograph for extended release capsules of diltiazem hydrochloride. Drug release from a heterogeneous lipid matrix such as that of formulations F3 and F4 is combined effect of drug leaching which occurs as the dissolution medium penetrates the matrix through pores, cracks and intragranular spaces as well as erosion of the matrix which is facilitated by the saponification of fatty acid by the alkaline intestinal milieu. Figure 1 compares the drug release behaviour of various hot melt extruded-spheronized pellet formulations of diltiazem hydrochloride.

Figure 2 is SEM micrograph of hot melt extruded and spheronized pellets of diltiazem hydrochloride which illustrates the morphological features of bead surface at low magnification. The HME bead exhibited surface indentation, although no granular characteristics were observed as noted with beads produced by hot melt extrusion. Surface indentation could be because of non-uniform or non-homogeneous contraction of lipid(s) during congealing stage resulting in formation of shallow craters. It can also be attributed to heterogeneous nature of the lipid matrix.

In vitro dissolution studies performed on pellets kept at accelerated storage conditions (stress stability) up to 3 months demonstrated no change in impurity profile, drug content and drug release rates.

Conclusions

Spherical pellets were successfully manufactured by a HME and spheronization process. HME and spheronization is a continuous process and does not require a lengthy drying step due to the absence of water or other solvents during manufacturing. Melt-extruded pellets exhibited a narrower particle size distribution in comparison with pellets prepared by conventional wet-mass extrusion. The pellets prepared by conventional wet extrusion or by drug layering in Wurster and then drug release controlled by coating do not follow the drug release as per USP Test No 5. HME pellets do not require a polymeric coating layer to prevent rapid drug release. Melt-extruded pellets can be additionally modulated to control drug release in the gastrointestinal tract. Owing to freedom from use of solvent during processing as well as short processing time, the products exhibited greater physicochemical stability. In conclusion, hot-melt extrusion-spheronization offers an attractive alternative to membrane-coated pellets in the development of controlled release multiparticulate dosage forms.

References

1. Berner, B. and Dinh, S., Fundamental concepts in controlled release. In: Treatise on Controlled Drug Delivery (Kydoneus, A., ed.), Marcel Dekker Inc, NY, 1992.
2. Ghebre-Sellassie, I., Pellets – A general overview, Pharmaceutical Pelletization Technology, Marcel Dekker Inc., New York, 1989, 1-13.
3. Chen, C.M., Diltiazem controlled release formulation, US Patent 5834023, 1998.
4. Follonier, N., Doelker, E. and Cole, E.T., Evaluation of hot melt extrusion as a new technique for production of polymer based pellets for sustained release capsules containing loading of freely soluble drug, Drug Dev Ind Pharm, 1994, 20, 1323-1339.
5. Goskonda, S.R. and Upadrashta, S.M., Avicel RC-591/chitosan beads by extrusion/spheronization technology, Drug Development and Industrial Pharmacy. 1993, 19, 815-927.
6. Prodduturi, S., Urman, K.L., Otaigbe, J.U. and Repka, M.A., Stabilization of hot-melt extrusion formulations containing solid solutions using polymer blends, AAPS PharmSciTech, 2007, 8, E1-E10.
7. Case, C.C., Melt pelletization. In: Pharmaceutical Extrusion Technology (Ghebre-Sellassie, I. and

Martin, C., eds.), Marcel Dekker Inc., New York, 2003, 99-110.
8. Erkoboni, D.F., Extrusion/Spheronization. In: Pharmaceutical Extrusion Technology (Ghebre-Sellassie, I. and Martin, C., eds.), Marcel Dekker Inc., New York, 2003, 277-322.
9. Zhang, F. and McGinity, J.W., Properties of hot-melt-extruded theophylline tablets containing poly(vinyl acetate). Drug Development and Industrial Pharmacy. 2000, 26, 931-942.
10. Diltiazem Hydrochloride Extended Release Capsules, USP32-NF27, The United States Pharmacopeial Convention, Maryland, USA, 2009, 2159-2165.

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