Application of Hot-Melt Coating Process for Designing a Lipid Based Controlled Release Drug Delivery System for Highly Aqueous Soluble Drugs

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Hot-melt coating process (HMCP) was applied to develop a lipid based oral controlled release matrix system (tablet) to deliver highly aqueous soluble drugs using paracetamol as a model drug. Granules prepared from paracetamol and particular filler were coated with different levels of lipid and then compressed into tablets to get controlled/sustained delivery of the drug over an optimum period. Process parameters were optimized with particular focus on fluidization pattern during HMCP proposing a 'design space' with 'Quality by Design' (QbD) concept in mind. The results demonstrated that the granule composition influenced the drug release pattern, and the rate of release could be manipulated by varying the amount of lipid in the formulation. The *in vitro* release profile of the drug was pH-independent and the most promising release profile was obtained from tablets prepared from granules with the water-soluble filler, lactose, and coated at 9% (w/w) level with a lipid, glyceryl behanate. *In vivo* plasma profiles of the drug were predicted from the *in vitro* release profile data by convolution analysis which confirmed that the lactose based formulation with 9% (w/w) lipid coating on the granules would be suitable for controlled delivery of the drug over a period of 12 h making the formulation suitable for highly water soluble drug candidates like paracetamol with twice daily dose regimen. Moreover, the dissolution data adequately fitted into Higuchi model suggesting that the drug release occurred predominantly by diffusion.

Key words hot-melt coating process; controlled release; design space; pharmaceutical product design; lipid matrix; paracetamol

Fluid bed coating process has been widely used in chemical and pharmaceutical industries because the process can be applied for coating cores of various sizes starting from small particles (hundreds of microns) to considerably large size objects like tablets and capsules (few centimetres). Also, the availability of improved versions of equipment for the purpose made it possible to scale up the lab-based process with ease to suit commercial scale manufacture of the products ensuring effective and reproducible coating process. Although the fluid bed coating process involves more than 20 parameters, establishment of optimal fluidization pattern is still the central point of the process to achieve homogenous level of coating to the cores and to achieve satisfactory uniformity of content in the final product.[1)] This is particularly important for hot-melt coating process (HMCP) because it is a rapid process where coating material is used melted without any solvent and applied within very short time directly to fluidized cores.

Organic solvents have now become outdated for the purpose of coating because of environmental concerns and hence, alternatives have been developed using aqueous polymeric dispersions.[2,3)] Potential problems with such systems have also been reported like penetration of water to the substrate core, microbial contamination, migration of hydrophilic drug through the polymeric film and physico-chemical instability.[4)] In addition to aqueous polymers, lipids have also been used as coating materials to develop sustained and/or controlled release drug delivery systems.[5—9)]

Lipids in general have been extensively studied for their use to deliver drug in controlled/sustained release manner starting from experimental use by Shear in 1936 to deliver a carcinogen from a cholesterol based implant to induce tumours in mice[10)] with many subsequent reports for its use to deliver therapeutic[11,12)] and prophylactic substances.[13,14)] While lipid based controlled release systems have been developed successfully for insoluble or slightly soluble drugs, development of similar system for highly aqueous soluble drugs still remains a challenging task; and due to the fact that lipids have specific physical properties and are distinctive from other commonly used excipients (like polymers), they are difficult to incorporate into formulation in quantities suitable for controlled/sustained release products. As a result, the pharmaceutical scientists have reported different ways of incorporating lipids into oral controlled/sustained release formulations like HMCP,[5—8)] organic solvent coating process,[9)] physical mixtures and solid dispersions of drugs and lipids,[15—17)] melt granulation,[18,19)] and lubrication.[20)] When compared with HMCP, these other approaches require significantly more lipid material for similar sustained release profile, which can be a limiting factor for high dose drugs. Also, such excessive amount of lipid in the formulation can induce pronounced problems through curing and aging (like significant release retardation, stability problems, *etc.*). Moreover, the lipid used for direct mixing with the drug and/or other excipients must be processed in advance to have some adequate properties like high melting point, adequate flowability, granular form, compressibility and the like, to be compressed into tablets, which is not the case for lipids used in HMCP.[21)]

The previous studies reported on HMCP[5—8)] were predominantly focused on properties of the final product (granules, beads or tablets) with demonstration of its usefulness in controlled/sustained release drug delivery systems. Although the authors noted some limitations of the process, like incomplete coating of granule surface, there was no attempt to apply integrated approach on product, process and possible application; namely to characterize the fluidization pattern

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during HMCP, asses quality of obtained product and/or to predict *in vivo* performance. Such integrated approach is known as 'chemical product design' in the field of chemical engineering. This has been an area of significant research interest during the last few decades with potential for practical application.[22,23] Similar approach in the field of pharmaceutical technology is known as 'Quality by Design' (QbD), which has now become a global regulatory focus for new product development. The QbD concept gives particular importance to process optimization and preformulation studies to ensure predefined quality of the finished product.[24]

The main objectives of this work reported here were: (i) to evaluate the suitability of HMCP for designing a lipid based controlled/sustained release oral drug delivery system (tablets) for highly aqueous soluble drugs using paracetamol as a model drug to achieve release over an extended period of about 12 h for improved patience compliance, and (ii) to apply integrated approach on formulation development and manufacturing process for the system with QbD concepts in mind. Glyceryl behanate was used as the lipid to control the release process because of its chemical inertness and adequate physical properties (good glidant with melting point above 70 °C).[20]

The *in vitro* drug release data were also analyzed using Higuchi diffusion model[25,26] to evaluate the release mechanism of the tablets. Moreover, pharmacokinetic properties including plasma profiles of the drug released from the tablets were predicted to evaluate suitability of the designed drug delivery system for its practical application in humans.

Experimental

Materials Paracetamol was supplied from King Kong Chemical Group, China. Dicalcium phosphate dihydrate (Calipham®), microcrystalline cellulose (Avicel® PH 101) and lactose (Fast Flo®) were obtained from Albright & Wilson (U.K.), FMC (U.S.A.), and Seppic (France), respectively. The lipid coating material, Glyceryl behenate (Compritol® 888 ATO), was supplied by Gattefosse (France), and the binder, polyvinylpyrollidone (PVP K-30), was supplied by Bayer AG (Germany). All chemical reagents used were of analytical grade.

Preparation of Granules and Tablets Paracetamol granules containing the drug at 80% (w/w) level were prepared by standard wet granulation method in laboratoy scale using a planetary mixer. The granules were dried in a tray oven and screened through 630 μm sieve prior to coating. In addition to paracetamol, the granules contained a filler—either microcrystalline cellulose (samples code 'A') or dicalcium phosphate dihydrate (samples code 'F') or lactose (samples code 'L'). All the granules had the same amount (w/w) of the excipients: 17% (w/w) of the filler and 3% (w/w) of PVP K-30 as binder. The granule compositions are presented in Table 1.

Equipment and Hot-Melt Coating Process A fluid-bed granulator (Glatt, WSG 3) was modified and used for the intended purpose of HMCP as part of QbD with possible process analytical tools. Three controllers were installed in the apparatus to regulate the inlet air temperature (T_i), quantity of fluidizing air (F_a) and spraying rate of the molten material (F_m). Preheated atomized air (20—30 °C above melting point of the coating material) was used for spraying the molten material through a binary nozzle. The nozzle construction ensured molten material to be surrounded by hot air throughout the process and an oscillating needle additionally supported fine atomization of the molten material. External path of the molten material from the container to apparatus was heated by an IR heater. The coating material was sprayed from the top to fluidized granules. Process parameters such as fluid bed temperature (T_b), outlet air temperature (T_o) and atomization pressure in binary nozzle (p_n) were set according to the coating material (melting/solidification) properties and equipment capabilities (p_n). These parameters were recorded throughout the coating process. Geometry of coating chamber was conical with inlet conus diameter (D_i) of 0.2 m, outlet conus diameter (D_o) of 0.3 m and height of conical part (l) of 0.25 m. Since HMCP is a relatively short process, the fluidization pattern was viewed as critical, and was controlled through related fluidization parameters: height of fluidization (L_f), fluid bed porosity (ε) and pressure drop during coating process (Δp). Fluidized particles (granules) were classified as per Geldart's particles classification chart to demarcate type and pattern of fluidization. Granules of all compositions were coated at three different levels: 3% (w/w) (samples codes A2, F2, L2), 6% (w/w) (samples codes A3, F3, L3) and 9% (w/w) (samples codes A4, F4, L4). The weight gain during the coating process was monitored in comparison with uncoated granules used as controls (samples: A1, F1, L1). All granule compositions are listed in Table 1.

Calculated amount of coated granules were compressed into tablets to contain 300 mg and 350 mg of paracetamol using a single punch tablet press with round and shallow concave punches, 10 mm in diameter.

Fluidization—Theoretical Considerations Fluidization pattern has been comprehensively described and established by Geldart[27]; this is known as Geldart's classification chart. He was the first one to classify the behaviours of fluidized solids (in gases) into 4 clearly recognizable groups characterized by density and mean particle size of fluidized particles, which has become standard to demarcate the fluidization pattern. Once optimal fluidization pattern is established, the process was controlled by three main parameters: height of fluidization (L_f), fluid bed porosity (ε) and pressure drop during coating process (Δp).

Height of fluidization (L_f), the highest distance that granules were reaching before falling and recycling, was kept constant, that was equal to the height of conical chamber of the apparatus. Moreover, L_f/d_p, a dimensionless parameter that combines particles parameter (d_p) with the equipment geometry/fluidization height (L_f) was calculated, as was found useful for prediction of porosity during fluidization in conical geometry.[1,28] Fluid bed porosity (ε) is the ratio (Eq. 1) between the volume occupied by air (corresponding to total volume minus volume of fluidized particles/granules or $V_t - V_p$) and total volume of coating zone of the apparatus (V_t):

$$\varepsilon = (V_t - V_p)/V_t \quad (1)$$

Pressure drop ($\sum \Delta p$) is result (Eq. 2) of empty apparatus resistance (Δp_0) and of the particles/granules themselves (Δp):

$$\sum \Delta p = \Delta p_0 + \Delta p \quad (2)$$

Δp is a function (Eq. 3) of several parameters like granules gravity (g), density of air (ρ_z) and granules/particles density (ρ_p), fluid bed porosity (ε) and height of fluidization (L_f):

$$\Delta p = g \times (\rho_p - \rho_z) \times (1 - \varepsilon) \times L_f \quad (3)$$

These mathematical equations for bed porosity and pressure drop (Eqs. 1—3) were previously found adequate by us[28] to predict values of fluidization parameters for system (pharmaceutical substrate) and apparatus geometry similar to the one used here.

Analysis of Granules and Tablets Paracetamol content in coated and control (uncoated) granules was determined spectrophotometrically (CAMSPEC M330, at $\lambda = 243$ nm) using a validated method. About 400 mg granules were grounded into fine powder and transferred into flask, then stirred in 900 ml of 0.1 N HCl at 37 °C for 4 h. A 3 ml sample was collected, filtered and assayed for paracetamol content.

Size distribution of the granules were determined by light scattering method (Malvern, Master Sizer X) on solid sample system—before, during and after coating. Granulometry parameters were calculated by supporting software (all data not shown).

Flow properties of the granules were determined by pouring 100 g of granules through 1-cm funnel orifice. Tapped (ρ_t) and untapped (ρ_o) granule density were also measured. Compressibility percentage was calculated according to Carr index equation[29]:

$$C\ (\%\ \text{compressibility}) = 100(\rho_t - \rho_o)/\rho_t \quad (4)$$

The tablets were evaluated for friability (Erweka tester, TAR 10), hardness (Van Kel tester, VK 200).

***In Vitro* Release Studies** The USP basket method (100 rpm, 37 °C) using an USP dissolution apparatus I (Prolabo, France) was used to study the release profiles of the drug from the coated granules; but the USP paddle method using USP dissolution apparatus II was used for tablets. Enzyme free simulated gastric fluid (SGF) (pH 1.2), pH 4.5 buffer and simulated intestinal fluid (pH 6.8), were used as dissolution media to observe the impact of pH on the release profiles. The amount of paracetamol released at predetermined time points was calculated spectrophotometrically at $\lambda = 243$ nm. Mostly the data obtained from SGF are presented here because the release profile was found as pH-independent.

Table 1. Composition and Results of Analysis of the Granules and Tablets Compressed from These Granules

Compositions		Granule characteristics							Tablets	
Code	Components	E (%)	$d_{(50)}$ (μm)	$d_{(90)}$ (μm)	t_f (s)	ρ_o (g/ml)	ρ_t (g/ml)	C (%)	H (kPa)	F (%)
F1	Paracetamol, dicalcium phosphate dihydrate, PVP	0	211.94	495.68	11	0.58	0.65	10.76	4	1.50
F2	(F1)+3% compritol	2.97	319.53	538.53	9	0.53	0.58	8.62	4	1.50
F3	(F1)+6% compritol	5.90	354.59	548.80	8	0.55	0.60	8.33	7	0.86
F4	(F1)+9% compritol	8.65	531.74	586.90	8	0.51	0.55	7.27	8	1.26
A1	Paracetamol, microcrystalline cellulose, PVP	0	239.59	478.22	9	0.63	0.66	6.10	8	0.11
A2	(A1)+3% compritol	3.06	417.71	506.60	8	0.61	0.66	7.40	8	0.10
A3	(A1)+6% compritol	5.93	427.28	576.68	8	0.56	0.59	5.60	8	0.86
A4	(A1)+9% compritol	8.50	415.09	580.86	8	0.54	0.57	5.40	8	0.10
L1	Paracetamol, lactose, PVP	0	272.71	529.41	11	0.46	0.52	11.50	8	0.11
L2	(L1)+3% compritol	3.04	338.72	569.66	10	0.49	0.55	10.90	8	0.10
L3	(L1)+6% compritol	5.70	480.55	569.99	10	0.49	0.54	9.25	8	0.16
L4	(L1)+9% compritol	8.98	500.76	567.65	9	0.49	0.53	7.55	8	0.10

E, efficacy of coating process; $d_{(50)}$ and $d_{(90)}$, values for particle diameter (below which was 50% and 90% of particles, respectively); t_f, time of powder flow; ρ_o, bulk density; ρ_t, tapped density; C, Carr index; H, hardness; F, friability.

SEM Observations Microscopic observations of granules (uncoated and coated) were performed using a scanning electron microscope (SEM, Joel JSM-5800). Granules were gold coated and then observed at magnification of 45× and 110×.

Drug Release Kinetics *In vitro* release data were analyzed against Higuchi diffusion model[25,26] using Statistica® software. Linear regression analysis of the data was performed and model parameter slope (k) and coefficient of correlation (r) with related standard deviations were estimated.

Prediction of Plasma Profiles of the Drug and Pharmacokinetic Parameters Considering the fact that the A type tablets gave incomplete release after 12 h *in vitro* and it was very difficult to compress the F type granules into tablets with adequate and consistent physical properties, only the *in vitro* release profiles of all the L type tablets in SGF medium were evaluated by convolution analysis to predict plasma levels over time using a software program called QWERT (version 1.1, SI Computing, Uppsala, Sweden), as we have reported in a previous paper.[30] The software program is designed to perform convolution/deconvolution analyses as was originally reported by Langenbucher in 1982.[31] Recently published *in vivo* plasma profiles following oral administration of paracetamol solution[32] were used as weighing function with dose normalization to compensate for the difference between the published data and the studied tablets.

Results

Hot-Melt Coating Process and Fluidization The melted lipid kept at 90 °C with atomization air temperature of 100 °C and bed temperature of 70 °C sprayed at a rate of 6—7 g/min with binary nozzle pressure 1.2—1.3 bar gave quality granules for further processing.

Since hot-melt coating is a rapid process, it took only about 3.5, 7 and 10.5 min to reach 3%, 6% and 9% coating levels, respectively, in this experiment. Such short coating time emphasizes the need for optimal fluidization pattern with continuous recycling of every granule near nozzle and colliding with the coating material. After several preliminary trials where coating efficiency (E, as presented in Table 1) served as indirect criteria to distinguish optimal (losses of coating material below 5%) from non-optimal process (losses of coating material above 5%), the fluidization process was standardized. Geldart's chart obtained for every fluidization trial revealed that all experimental data are grouped in narrow zone (Fig. 1), which can serve as 'design space' according to the QbD concept.[24] The height of fluidization was kept constant with stabilized fluidized bed porosity in optimal narrow range. The L_f/d_p values decreased as the coating level increased for all three types of granules with an exception of the A4 granules (Table 2).

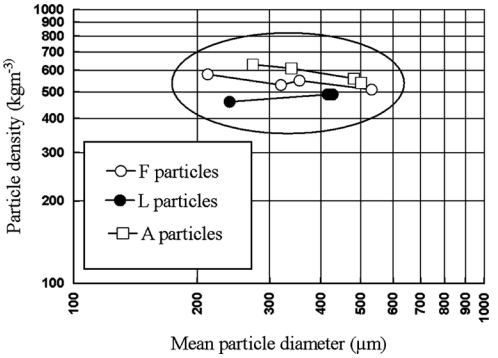

Fig. 1. Geldart's Chart for Fluidization of Different Particles (Granules) Based on Particle Density and Particle Mean Diameter with Proposed and Rounded 'Design Space' during HMCP

Air flow required adjustment as the HMCP was advanced (90—128 m^3/h) to maintain optimal fluidization pattern of enlarged and heavier coated particles. In line with air flow adjustment, air velocity was increased from around 90 m/s in the beginning of HMCP to 128 m/s at the end for A4 type granules. Uncoated particles had d_{50} in range of 210—270 μm, 3% coated above 300 μm, 6% coated 350—480 μm, 9% coated around 500 μm. Pressure drop raised up from initial value for uncoated granules (380 Pa for F1, 400 Pa for L1, 600 Pa for A1) up to twice as much at the end of HMCP when 9% lipid coating was applied (800 Pa for F4, 600 Pa for L4, 800 Pa for A4).

The optimized coating process had constant height of fluidization (L_f) of 0.25 m and fluidized bed porosity within the range of 89.5—91.5%. The summary of parameters and values that were used for calculation of fluidization pattern is presented in Table 2.

The suggested 'design space' (Fig. 1) and the data presented in Table 2 are evidence of controlled and standardized fluidization pattern, which also served as basis for further comparison of different granules characteristics.

Table 2. Parametres and Values That Were Used for Calculation of Fluidization Pattern

Granule	d_p (μm)	F_a (m^3/h)	v (m/s)	m (g)	L_f/d_p	ε (%)	Δp (Pa)
F1	211.94	89.6	2852	700	1179.6	91.34	380
F2	319.53	102.4	3259.5	700	782.4	90.29	400
F3	354.59	108.8	3465.2	700	705.4	90.19	600
F4	531.74	115	3660.6	700	470.1	89.76	800
A1	239.59	96	3055.8	700	1043.4	91.47	600
A2	417.71	105.6	3361.4	700	598.5	91.45	650
A3	427.28	115.2	3666.9	700	585.1	90.4	700
A4	415.09	128	4074.4	700	602.2	90.12	800
L1	272.71	95.8	3055.8	700	916.7	89.17	400
L2	338.72	102	3246.8	700	738.1	89.76	450
L3	480.55	108	3437.7	700	520.2	89.57	480
L4	500.76	118	3756.1	700	499.2	89.5	500

d_p, particle diameter; F_a, flow of fluidization air; v, velocity of air for fluidization; m, mass of fludized granules; L_f, height of fluidization; ε, fluidized bed porosity; Δp, pressure drop during fluidization. L_f/d_p represents a dimensionless parameter that combines particles parameter (d_p) with the equipment geometry/fluidization height (L_f) that was kept constant in all the experiments.

Granules and Tablets Some physical characteristics obtained for granules and tablets of compositions F, A and L are presented in Table 1. The coating efficacy data (E) demonstrate losses of less than 3.5% of the material during HMCP. In comparison to uncoated granules, the coated granules had improved flow properties: shorter time of flow (t_f) and also lower Carr index (C). Time of flow decreased for few seconds (1—3 s) and was ≤11 s for all coated granules (*e.g.*, 11 s for F1 granules, 8 s for F4 granules). Carr index was also reduced by 1—4% for coated granules comparing with initial index for uncoated granules (*e.g.,* 11.5% for L1 granules, 7.55% for L4 granules).

Scanning electron micrographs revealed irregular surface of granules prior to coating and uneven coating surface with noticeable holes even at the highest level of coating (Figs. 2a—c).

The dissolution profiles obtained in SGF from all three types of granules demonstrate that the coating level had significant impact on the release profiles and as the level of coating increased the release rate was significantly reduced (Fig. 3) with an exception of the granules prepared from lactose as filler at 3% coating level (Fig. 3c). Although the absolute values of the release profiles obtained for the three types of granules (at the same coating level) are significantly different when compared to each other, the relative patterns obtained for the three types of granules have similarities, *i.e.*, at higher level of coating the release profile was slower; as the coating level increased from 3 to 9%.

Granules prepared from microcrystalline cellulose (type A) and lactose (type L) were compressed without any difficulties and the tablets had good mechanical properties with desired level of hardness (8 kPa) and friability (<1%) (Table 1), but the granules prepared from dicalcium phosphate dihydrate (type F) did not compress smoothly; rather constant problem of capping and sticking to punches during compression occurred. Also, the tablets had poor mechanical properties with maximum hardness range of 4—8 kPa and poor friability (Table 1).

The *in vitro* release profiles obtained in SGF from the tablets compressed from granules prepared with dicalcium phosphate dihydrate (type F), microcrystalline cellulose (type A), and lactose (type L) are presented in Figs. 4a, b and c, respectively. At 3—6% coating levels the tablets did not show noticeable sustained release properties except the A type tablets. However, at 9% coating level all types of tablets demonstrated sustained release profiles over 12 h period, but with incomplete release (up to 60%) from A type tablets.

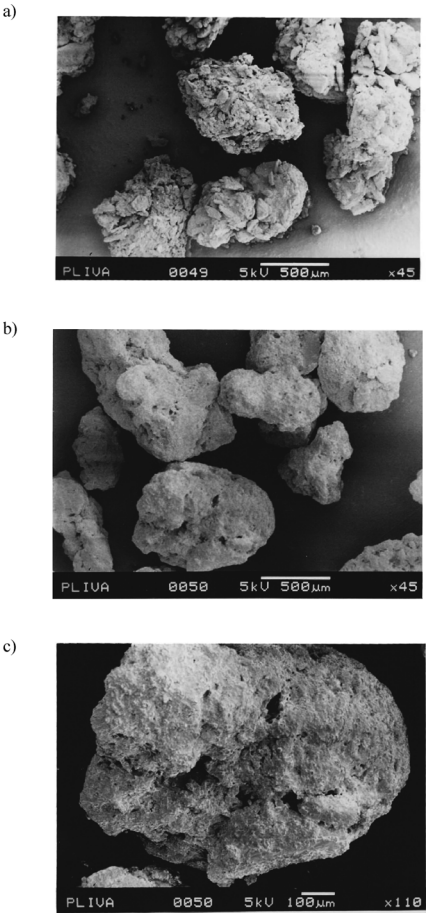

Fig. 2. SEM Images of L Type Granules: (a) Uncoated Granules (45×), (b) 9% Lipid Coated Granules (45×), and (c) 9% Lipid Coated Granules (110×)

The dissolution profiles obtained from the tablets prepared from all three types of granules at all three levels of coatings appeared to be faster than those obtained for the correspond-

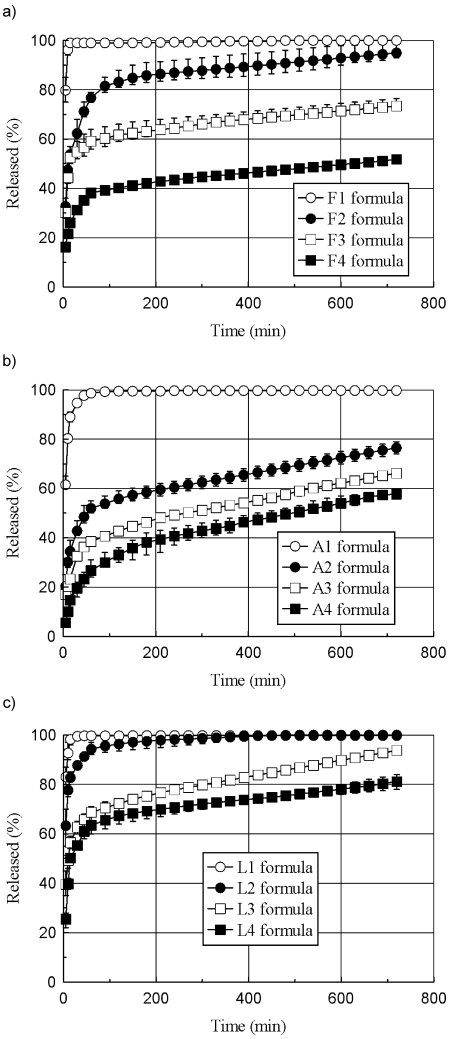

Fig. 3. Effect of Coating Level on *in Vitro* Drug Release from Control and Hot-Melt Coated Granules

F1, A1, L1, control granules; F2, A2, L2, 3% coating level; F3, A3, L3, 6% coating level; F4, A4, L4, 9% coated granules. The USP basket method using SGF as dissolution medium was used. Each point represents the mean value obtained from 6 samples and the vertical bars indicate standard deviation of the data (A, F type granules; B, A type granules; C, L type granules data).

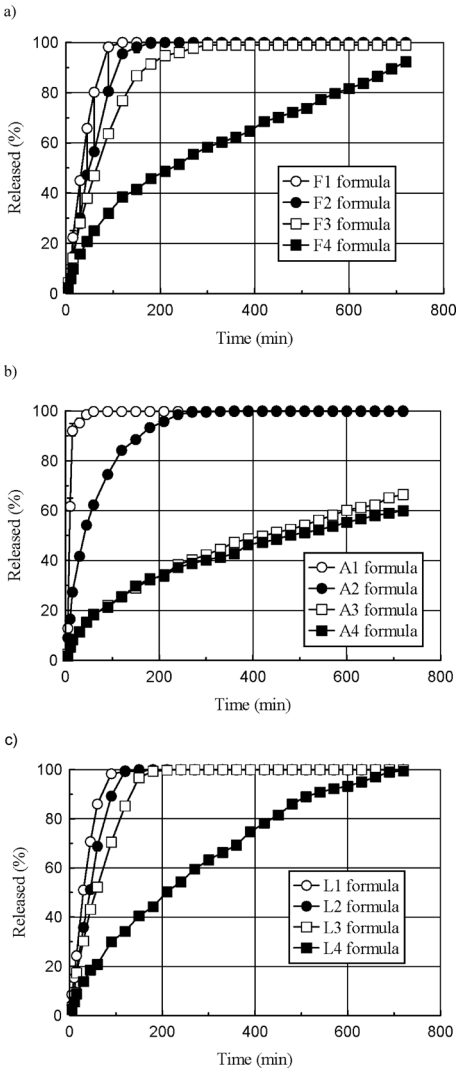

Fig. 4. Effect of Lipid Level on *in Vitro* Drug Release from Tablets Prepared from Control and Hot-Melt Coated Granules

F1, A1, L1, tablets prepared from control granules; F2, A2, L2, tablets prepared from 3% coated granules; F3, A3, L3, tablets prepared from 6% coated granules; F4, A4, L4, tablets prepared from 9% coated granules. The USP paddle method using SGF as dissolution medium was used. Each point represents the mean value obtained from 6 tablets and the vertical bars representing standard deviations are within the points where not visible. (A, F type tablets; B, A type tablets; C, L type tablets).

ing granules (Figs. 3, 4).

From the *in vitro* profiles obtained in SGF medium, L4 tablets were selected as the most promising ones for further testing in other dissolution medium to study any impact of pH of the dissolution media since sustained release products are designed to pass through the entire pH range (1.0—8.0) of the gastrointestinal tract.[33] The *in vitro* profiles obtained in other media demonstrate that the release profiles from these tablets are in line with those obtained in SGF and they are pH-independent (Fig. 5).

Drug Release Kinetics The *in vitro* data tested against Higuchi model with subsequent linear regression analysis are presented in Table 3. The release rate constants (k) values decreased as the lipid level in the tablets increased. The coefficient of correlation (r) values obtained from linear regression analysis were ≥ 0.99.

The dissolution profiles were also tested using first-order kinetics model (data not shown) but the parameters obtained were inferior to those obtained from the Higuchi model.

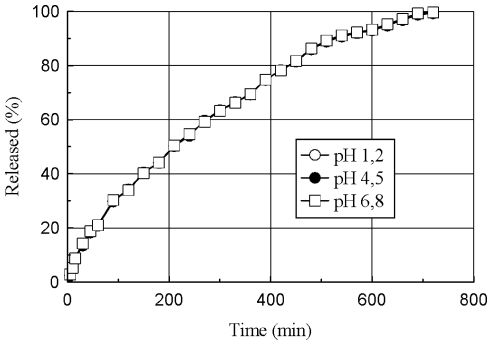

Fig. 5. Effect of Dissolution Medium pH on *in Vitro* Drug Release Profile from L4 Tablets

Each point represents the mean value obtained from 6 tablets and the vertical bars representing standard deviations are within the points where not visible.

Table 3. Estimated Release Rate Constant (k) and Coefficient of Correlation (r) for the Higuchi Model with Corresponding Standard Deviations (S.D.) for All Tested Tablets

Tablet	r	S.D.	k	S.D.
F1	0.9965	0.0132	13.9647	0.1851
F2	0.9939	0.0152	10.3196	0.1583
F3	0.9828	0.0203	6.8871	0.1425
F4	0.9984	0.0043	3.4814	0.0152
A1	0.9959	0.0224	48.578	1.0947
A2	0.9794	0.0240	6.8660	0.1687
A3	0.9991	0.0032	2.5370	0.0083
A4	0.9973	0.0056	2.2941	0.0130
L1	0.9922	0.0197	13.5239	0.2685
L2	0.9955	0.0148	12.1020	0.1809
L3	0.9991	0.005883	9.5048	0.0559
L4	0.9981	0.004908	4.2255	0.0207

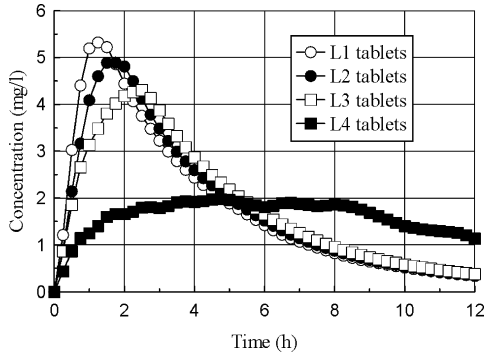

Fig. 6. Predicted Plasma Profiles Obtained by Convolution Analysis of the Dissolution Data Obtained from L Type Tablets in SGF Medium (Presented in Fig. 4c)

Convolution Analysis The predicted plasma profiles obtained (using *in vitro* profiles presented in Fig. 3c as input functions) from the L type of control tablets (L1, without lipid) and tablets prepared with different levels of lipids are presented in Fig. 6. The C_{max} and $AUC_{(0—t)}$ values calculated from the predicted plasma profiles of the control tablets are 5.32 mg/l and 22.58 mgh/l respectively which represent above 95% of the corresponding values obtained from oral administration of paracetamol solution[32] after dose normalization. Also, these data calculated for control tablets are in good agreement with C_{max} and $AUC_{(0—t)}$ for Tylenol® caplets (325 mg paracetamol) as presented in Patient Information Leaflet and drug clinical pharmacology data for the product. The C_{max} values obtained for tablets prepared from granules coated at 3% and 6% levels are 4.89 mg/l and 4.31 mg/l with corresponding $AUC_{(0—t)}$ values 22.54 mgh/l and 22.43 mgh/l, respectively. But the tablets prepared from granules coated with 9% lipid gave an exemplary sustained release profile of the drug with a rapid increase of the plasma level within 30 min reaching a plateau level in less than 90 min keeping it at a constant level over 8—9 h period before declining, giving an $AUC_{(0—t)}$ value of 19.43 mgh/l.

Discussion

The predicted plasma profiles and pharmacokinetic parameters obtained from the control tablets (without any lipid) are in line with literature report for immediate release paracetamol tablets; and the fact that the predicted C_{max} and AUC values represent about 95% of the paracetamol oral solution data,[32] it gives a reasonable degree of confidence on the data obtained for the L4 tablets which demonstrate that a plateau level of the drug could be reached within about 90 min and kept over a prolonged period of 8—9 h at the same level. Moreover, the predicted $AUC_{(0—t)}$ value obtained for these tablets are in agreement with the AUC values obtained for the other formulations and those reported in literature. In fact, we have previously demonstrated the reliability of convolution analyses in predicting plasma profiles by comparing the predicted profiles with *in vivo* data obtained from studies in humans.[30] The predicted plasma profiles from L4 tablets clearly demonstrate that the developed matrix system (tablet) would be suitable to deliver highly water soluble drugs like paracetamol for twice daily dose regimen following oral administration. Indeed the predicted plasma profile obtained for L4 tablets resembles text book example for controlled/sustained release products, and it is apparent that a trickle delivery of the drug occurs after reaching a peak level for a prolonged period with simultaneous elimination almost at the same rate, which is optimal condition for sustained release products.

From the QbD perspective, the HMCP trials conducted with process parameters within the design space ensured good quality of fluidization and very efficient coating material deposition process on the cores. Fluidized particles at operating conditions of HMCP demonstrate characteristics of Geldart group A particles.[27] This group is ideal for smooth and good quality fluidization; it is characterized with high solid/gas mixing and good bed expansion.

The coating levels determined for all three types of granules were almost the same as theoretically expected from the levels of the lipid applied for coating demonstrating good coating efficacy (E). The losses observed were less than 3.5% as maximum which demonstrates that the HMCP run smoothly, process parameters were optimized appropriately and a proper design space for fluidization has been proposed (Fig. 1). As expected, the higher level of coating material produced large granules (Table 1) subsequently reducing the L_f/d_p values except for A4 type granules, which appeared to have smaller particles (d_{50}) with 9% coating level than 3% and 6% coating levels (Table 2). When compared to uncoated granules, the coated granules had improved flow properties, *i.e.*, shorter time of flow (t_f) and lower Carr index (C). This is not surprising since lipids are known for their use as glidant.

The *in vitro* profiles obtained from coated granules in SGF (Fig. 3) are typical for this type of products—control of the release process is inadequate characterized by burst release within first 15—30 min followed by very slow and incomplete release at the end.[6,7] The inadequate release profile, specifically the initial burst release is attributable to the properties of the core granules because they had uneven surface to start with HMCP as evident from the SEM data (Fig. 2a), and the wide size distribution. Such physical properties of core granules seem logical because they are product of standard wet granulation process. Moreover, HMCP is a rapid process and hence coating time is in direct correlation to number of cycles that granules were exposed to sprayed molten material at the vicinity of the nozzle. All coated granules, even those with highest percentage of coating (9%), had uneven coating layer with visible holes and uneven surfaces

(Figs. 2b, c). As anticipated, the higher level of coating material produced slower release profile from the granules—logically ordered in terms of release retardation (Fig. 3) from uncoated, to 3%, 6% and 9% coating levels. The influence of filler type is also evident from the release profiles: 80% released from L4 granules *versus* 50—60% released from F4 and A4 granules at the end of 12 h dissolution run. This is attributable to the solubility properties of the filler itself since the L4 granules contained the soluble filler, lactose, and the other fillers are insoluble in water, and uneven coating surface prompted faster penetration of water into these granules through weak points that solubilised the filler and the drug at a faster rate than in the other granules.

The incomplete release of the drug from all three types of coated granules (at 3%, 6% and 9% levels) at the end of the dissolution runs after 12 h is probably due to entrapment of the drug within some coated granules where the lipid coating might have been excessive and acted as a barrier for penetration of the dissolution medium to solubilise the drug to diffuse. Moreover, the agitation force used in these experiments might not have been adequate enough to achieve complete release of the drug since the USP basket method is generally considered less discriminatory than the paddle method. The exceptional behaviour of L2 granules can be explained as due to the filler solubility characteristic in aqueous media.

Hardness and friability data (Table 1) suggest superiority of microcrystalline cellulose and lactose as fillers over dicalcium phosphate dihydrate in this particular combination but this does not necessarily disqualify dicalcium phosphate dihydrate as filler since addition of other excipients in the formulation to improve compressibility has not been attempted in this study.

The pattern of *in vitro* release profiles obtained from the tablets in SGF (Fig. 4) were as anticipated—tablets with higher level of lipid material demonstrated slower release profiles, which means that the drug release could be manipulated by varying the amount of lipid. In general, the tablets produced more pronounced controlled delivery profile than the corresponding granules: initial burst release was significantly reduced, followed by faster release than from corresponding granules, particularly at lower levels of coating. Most importantly, the release process was complete at the end of the dissolution runs (12 h) from almost all the tablets (except A3 and A4 tablets). The compression process appeared to have contributed to proper and uniform matrix formation due to 'redistribution' of the lipid material within the matrix. In addition, the USP paddle method might have played a role in the apparent faster and complete release of the drug from the tablets when compared to the corresponding granules which were tested by the basket method.

The most encouraging results are the *in vitro* profiles obtained from tablets with 9% (w/w) lipid in the inner matrix prepared using dicalcium phosphate dihydrate (F4) and lactose (L4) as fillers. Taking into account the difficulties associated with compression of F4 tablets and their poor physical properties (Table 1), the L4 tablets gave overall the most promising data set including *in vitro* release profile with 33% of the release in 90 min and controlled delivery of the drug over a 12 h period. The remaining 66% of the dose was linearly released during next 9—10 h achieving 100% release at the end of 12 h. Nevertheless, the *in vitro* release profiles obtained from A3 and A4 tablets suggest that it might be feasible to obtain optimum controlled release profile of the drug with lesser amount of lipid in the formulation from this type of tablets than L4 (or F4) tablets.

As discussed earlier for the granules, the filler type had impact on release profiles of the drug from the granules, even more significantly from the tablets. Although the F4, A4 and L4 tablets had the same level of (9%) of lipid material in the inner matrices, their corresponding *in vitro* profiles significantly differ. Lactose being more water soluble compound (solubility 189 mg/ml) than paracetamol (solubility around 20 mg/ml), was probably solubilised quickly creating pores in the matrix for the dissolution media to penetrate rapidly enabling faster dissolution of the drug, but at higher lipid level (9%) the retardation effect of the lipid was effective and optimum to get control of the release process over 8—9 h. This effect was particularly important for second part of the release profile of L4 tablets (period 2—12 h). Microcrystalline cellulose as a large chain molecule is insoluble in water, but is highly hygroscopic and a good matrix forming agent. As a result, tablets with composition 'A' had strong inner matrix formation of both lipid material and the insoluble filler. Consequently, *in vitro* release profiles even with only 6% of lipid material, released only around 60—70% of drug after 12 h. However, the control tablets (A1) gave almost instant release of the drug (100%) within 10—15 min because the filler is highly hygroscopic and promotes fast penetration of aqueous media into the matrix. The other filler used in the study, dicalcium phosphate dihydrate, is a small molecule substance and almost insoluble in water (0.2 mg/ml), but it is neither hygroscopic nor a good matrix forming agent. This explains why there was compressibility problem with the F type granules and slower release profiles of the tablets than those obtained from L type tablets.

The scale up of the tablet dose (and weight) for L4 tablets from 300 to 350 mg did not show any abnormality in terms of manufacturing and quality of the final products suggesting robustness of the formulation and manufacturing process.

The good fit of the dissolution data into Higuchi model suggests that the drug release occurs predominantly through diffusion from the matrix because the Higuchi model assumes that small drug particles are dispersed in insoluble, non-swelling matrix from which the release is limited by the rate of diffusion of the drug.[25,26] The product and process parameters presented in this report will be further tested to develop an engineering model for designing optimal controlled release pharmaceutical product using HMCP.

Conclusion

The data presented here demonstrate that a lipid based oral controlled release drug delivery system is feasible using HMCP and the system has application on highly water soluble drugs like paracetamol as candidates for twice daily dose regimen for better patient compliance. The recommended 'design space' for fluidization and optimization of other process parameters emphasizes the usefulness of the designed drug delivery system from practical view point, *i.e.*, manufacturing in commercial scale to benefit the patients at large. The tablets could be manufactured with ease and HMCP eliminates some of the problems encountered when the lipid is mixed with the drug/excipients either through

melting or direct mixing. Furthermore, the predicted plasma profiles of the drug obtained from the developed system by convolution analysis demonstrate its significance and suitability for practical use in humans from the biopharmaceutics view point and give a reasonable degree of confidence on reliability of the designed drug delivery system.

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