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Low density porous carrier Drug adsorption and release study by response surface methodology using different solvents

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Abstract

Low density porous carriers are widely used in the pharmaceutical applications. Response surface methodology, using 3^2 factorial design was used to study drug adsorption on and its release patterns from microporous polypropylene (Accurel MP 1000®) in the absence of additives. Ibuprofen, as model drug, was adsorbed on the polymer by solvent evaporation using two organic solvents methanol (M) and dichloromethane (DCM). The amount of carrier (100 mg) and its particle size range (250–350 μm) were kept invariant while solvent volume (X_1) and drug amount (X_2) were taken as variables. Drug adsorption pattern depended on the type and amount of solvent used. DSC, XRD, FTIR and TGA, predict crystalline nature and physical form of adsorption. SEM showed the penetration and adsorption of the drug in and on the microporous polymer. Accurel MP 1000® had a pore volume of 1.992 g/cm^3 and surface area of 55.9855 m^2/g as detected by mercury porosimetery. On drug adsorption, pore volume ranged from 0.413 to 1.198 g/cm^3 for methanol and 0.280–0.759 g/cm^3 for DCM. Similarly surface area was in the range 38.445–25.497 m^2/g for methanol and 18.710–32.528 m^2/g for DCM. The drug release was investigated in phosphate buffer pH 7.2. All batches showed excellent *in vitro* floating property. Drug release was partial with recovery to complete dependent on type and volume of solvent. R^2 values relating to bulk density, pore volume, surface area and drug release at 60, 120 and 180 min were estimated. Effect of solvent properties shows a positive influence on drug adsorption and release. Release profiles of some batches could be considered as gastroretentive drug delivery system.

Keywords: Microporous polymer; Carrier; Solvent evaporation; Response surface methodology; 3^2 factorial design

1. Introduction

Pharmaceutical research has taken a giant leap by providing various novel alternatives to the conventional drug dosage system. With the introduction of new polymers and other materials there has been a constant upgradation of drug delivery system to impart benefits to patients (Müller et al., 2000; Chilkoti et al., 2002; Liu et al., 2003; Berger et al., 2004; Packhaeuser et al., 2004; Lu and Chen, 2004). During the past decade, a diversity of inert polymeric carriers have been developed to control temporal or distributional drug delivery for oral, pulmonary, transdermal and injectables. Recently, there has been exponential growth in the investigations related to the use of porous material as controlled drug delivery matrices because of possessing several attractive features, such as stable uniform porous structure, high surface area, tunable pore sizes with narrow distribution and well defined surface properties. This allows them to adsorb drugs and release them in a more reproducible and predictable manner. Various types of drugs with small and large molecular size have been evaluated in developing delivery system (Song et al., 2005; Salonen et al., 2005; Ohta et al., 2005; Shivanand and Sprockel, 1998).

The use of mesoporous, microporous and nanoporous carriers for drug delivery is a part of ever growing research (Song et al., 2005; Li et al., 2004; Andersson et al., 2004). Type and extent of interaction of modified surface of porous carrier with water characterizes them as either hydrophobic or hydrophilic. Examples of pharmaceutically exploited porous carriers include porous silicon dioxide (Sylysia® 550, 320), polypropylene foam powder (Accurel®) (Streubel et al., 2002, 2003); porous calcium

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silicate (Florite®) (Murakami and Yata, 1995); magnesium aluminometa silicate (Neusilin® S2, NS2 N, US2) (Ito et al., 2005); porous ceramic (Byrne and Deasy, 2002); $CaCO_3$ (Wang et al., 2006); etc. Various drug loading methods reportedly use stirring in drug solution or suspension, immersion for long times till equilibrium is reached, using vacuum, emulsion formation, gravimetric method and solvent evaporation to contain drug within the carrier (Li et al., 2004; Otsuka et al., 2000; Ohta et al., 2005; Streubel et al., 2002, 2003).

A number of processes together make up during adsorption and mass transfer for drug release from porous materials. In and after contact with solvent, the drying that takes place involves many pore scale mechanisms such as the motion of individual gas–liquid meniscus residing in the pore spaces, diffusion in gas and liquid phase, capillarity and possible flow through connected films, etc. (Yiotis et al., 2001). Preferential flow in the porous material for adsorption or diffusion is influenced by pore structure and its network, boundary conditions and the physical characteristics of the porous material. Liquid penetration into and its subsequent flow through such porous material depends on both the molecular and bulk properties of the liquid and the geometric and surface property of the porous medium. The required displacement depends upon the pore size, surface tension of liquid and the contact angle between surface and liquid. The rate of pore volume variation by dissolution of drugs or solids in porous media is directly related to several driving forces or factors like (1) deviation of saturation ratio from unity indicates under saturation, equilibrium and supersaturation. (2) Volume of pore fluid. (3) Pore surface area having affinity for dissolution/precipitation (Civan Faruk, 2001). When porous hydrophobic polymeric drug delivery system is placed in contact with the appropriate dissolution medium, release of drug to medium must be preceded by drug dissolution in the water filled pores or from surface and by diffusion through the water filled channels. The geometry and the structure of the pore network are important in this drug release process (Gurny et al., 1982).

The influence of solvent polarity on the adsorption of drug into porous silica has been mentioned (Ohta et al., 2005). Adsorption of ibuprofen into inorganic porous materials such as silica gel in form of MCM-414, aerosol and $CaCO_3$, using solvents of varying in polarity, as expressed by dielectric constant, has indicated that drug adsorption increase with the decrease in solvent polarity (Charnay et al., 2004; Wang et al., 2006). In untreated and treated inorganic materials surface properties play an important role in drug adsorption and release such as silanol groups in silica based carriers. Drug release from porous cellulose matrices may be complete within 10 min (Gren et al., 1996); or be incomplete after several hours as in MCM family (Charnay et al., 2004); or days as observed with stens comprising of Accurel (Boer and Krusinbrink, 1987). Overall drug release from porous carriers is governed by the dominance of erosion and diffusion as with biodegradable materials (Lemaire et al., 2003); by either diffusion or dissolution or both for non-degradable materials which in turn is also influenced by the amount and solubility profile of the drug (Gurny et al., 1982). The release pattern is predominantly in a burst release followed by slow release unless modified.

Our work looks out at these processes for ibuprofen adsorbed on hydrophobic isotactic polypropylene based organic porous carrier, Accurel MP 1000®, characterized by open porous network with pore size predominantly in the micro and mesoporous range. This polymer has been evaluated for the development of floating drug delivery systems and stem development (Boer and Krusinbrink, 1987; Streubel et al., 2002, 2003). Ibuprofen, widely used as anti-inflammatory, hydrophobic and soluble in selected solvents was selected as the drug. No additive or coating was used to modify the drug release or adsorption process to determine and understand the release characteristic as if used as an uncoated carrier system.

The effect of the solvent used to dissolve the drug on adsorption process by solvent evaporation was investigated first. Two organic solvents, methanol (M) and methylene chloride (DCM) were selected on the basis of differing polarity index and boiling point. All studies were normalized to constant mass of porous carrier to minimize the effect of physical constants like porosity and the surface area, which influence adsorption process. 3^2 factorial design was applied to evaluate effect of the variables such as solvent and drug amount on drug release. Non-loaded and drug-loaded microparticles were characterized for micromeritic properties, practical yield, drug content and encapsulation efficiency, surface morphology by scanning electron microscopy (SEM), for crystallinity by differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD), for porosity by mercury porosimeter, FTIR, thermogravimetric analysis (TGA) and *in vitro* drug release in phosphate buffer pH 7.2.

2. Materials and methods

2.1. Materials

Accurel MP 1000 generous gift from Membrana (Germany), a low density microporous polypropylene microparticles with particle size <1500 μm, pore size in range from 5 to 20 μm and void volume of 70%. Ibuprofen, was a gift from Cipla (India). Methanol, dichloromethane (DCM) and other reagents were of analytical grade.

2.2. Preparation of drug-loaded beads

Ibuprofen was loaded onto the porous beads by solvent evaporation. Accurel MP 1000 was closely sieved in the range of 250–350 μm to nullify effect due to variation in particle size. In a typical study various amounts of drug was dissolved in the multiple volumes of solvent (methanol or DCM) followed by the constant addition of 100 mg Accurel MP 1000®, kept to evaporate solvent under ambient conditions.

2.3. Factorial design

We applied a 3^2 design to establish the inter-relationship between the selected variables. The variables studied were volume of solvent (X_1) and the amount of drug (X_2) at three different levels. The coded and the actual values of the experimental design are given in Table 1. The data analysis of values obtained

Table 1
Experimental variables of factorial design with their coded levels and actual values

Batches	Coded levels solvent (X_1), drug (X_2)	Solvent (mL) (X_1)	Drug (mg) (X_2)
1	−1, −1	1	100
2	−1, 0	1	200
3	−1, 1	1	300
4	0, −1	3	100
5	0, 0	3	200
6	0, 1	3	300
7	1, −1	5	100
8	1, 0	5	200
9	1, 1	5	300

from various batches for bulk density, pore volume, surface area and drug release at 60, 120 and 180 min were subjected to multiple regression analysis using statistical software UNISTAT® (statistic Version 3, Meglon US). The equation fitted was

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11}\ X_1^2 + \beta_{22} X_2^2 + \beta_{12} X_1 X_2$$

where Y: measured response; X: levels of factors; β: coefficient computed from the responses of the formulations.

2.4. Evaluation and characterization of microparticles

2.4.1. Yield and drug content

The dried weight of microparticles was recorded as practical yield. The drug-loaded beads were dissolved in methanol kept on ultrasonicator and drug content was assayed by determining in triplicate the absorption at 221 nm using UV-spectrophotometer (Jasco V500, Japan).

2.4.2. Differential scanning calorimetry

Thermograms of ibuprophen, Accurel MP 1000 and drug-loaded microparticles were obtained using a Mettler-Toledo DSC 821^e (Switzerland) instrument equipped with an intra cooler. Instrument was calibrated for DSC temperature and enthalpy using Indium standard. The samples were hermetically sealed in perforated aluminium pans and heated at constant rate of 10 °C/min over the temperature range of 25–150 °C. The system was purged with nitrogen gas at the rate of 100 mL/min to maintain inert atmosphere.

2.4.3. Surface topography

Microphotographs of the beads were observed at various magnification using scanning electron microscope (Cambridge Stereoscan 120, UK) operated with an acceleration voltage of 10 kV. The beads were mounted on the standard specimen mounting stubs and were coated with a thin layer (20 nm) of gold in sputter coater unit (VG Microtech, UK).

2.4.4. Powder X-ray diffraction

X ray powder diffraction patterns of drug, Accurel MP 1000 beads without and with drug were recorded by using a Philips PW 1729 X-ray diffractometer (Netherlands). Samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed at 2θ between 2° and 40°. The voltage and current used were 30 kV and 30 mA, respectively. The range and the chart speed were 5×10^3 CPS and 10 mm/2θ, respectively.

2.4.5. Fourier transform infra-red analysis

FTIR measurements of drug, Accurel MP 1000® and drug-loaded ones were obtained on JASCO FTIR 4000 (Japan). Samples were prepared by mixing with KBr and placing in the sample holder. The spectra were scanned over the wave number range of 3600–400 cm^{-1} at the ambient temperature.

2.4.6. Mercury porosimetry

Pore size and pore volume of Accurel MP 1000® without and with drug were evaluated using Autoscan 33 mercury porosimeter (USA). Samples were first loaded with mercury in a pressurized cell under vacuum and latter subjected to pressure range of 0–33,000 psi.

2.4.7. Thermogravimeteric analysis

The drug-loaded microparticles were subjected to gravimetric assay from 35 to 100 °C, with the heat flow of 5 °C/min using SEIKO model no. TG/DTA-32 (Japan). All experiments were performed in the presence of static air.

2.4.8. Dissolution studies

The dissolution of drug-loaded Accurel MP 1000® beads was studied using USP 26 Type II dissolution test apparatus (Electrolab TDT-06P, India) containing 900 mL of pH 7.2 phosphate buffer maintained at 37 ± 0.5 °C and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. Analysis of data was done using 'PCP Disso v2.08' software, India. All the readings were done in triplicate.

3. Result and discussion

3.1. Yield and drug content

All evaluations were at constant mass of porous polypropylene to minimize the effect of variation in pore volume and tortuosity on the related phenomenon like drug adsorption and release characteristics. The effect of particle size of polypropylene on release profiles has been established (Streubel et al., 2003). The constant amount and specific size range will help in better understanding the pattern of mass transfer taking place. The practical yield given in Table 2, ranged between 83 and 93% for methanol and between 89 and 100% for DCM. The drug content ranged between 81–89 and 92–100% for methanol and DCM, respectively. DCM having lower boiling point, less polar and low dielectric constant relative to methanol might have lead to high adsorption of drug over the hydrophobic surface. Similar trends between solvent type and drug adsorption have been reported. In relative performance of solvents differing polarity the maximum adsorption of this drug is due to least polar one (Wang et al., 2006; Charnay et al., 2004). Varying solvent volume also lead to difference in level of adsorption behavior governing drug content. The regression analysis establishes the influence of the drug amount and the solvent interaction for the

Table 2
Results of different evaluation parameters for drug-loaded porous microparticles

Batch	Practical yield (%)		Drug content (%)		Pore volume (g/cm^3)		Surface area (m^2/g)		Bulk density	
	m	d	m	d	m	d	m	d	m	d
1	95.0 ± 1.21	97.17 ± 1.33	85.43 ± 2.31	100 ± 0.16	0.897 ± 0.02	0.759 ± 0.01	36.47 ± 0.99	32.58 ± 0.78	0.513 ± 0.01	0.560 ± 0.01
2	87.33 ± 0.86	98.52 ± 1.65	85.85 ± 2.65	100 ± 0.21	0.565 ± 0.02	0.335 ± 0.01	31.64 ± 1.00	22.25 ± 0.89	0.622 ± 0.001	0.679 ± 0.002
3	83.50 ± 1.34	98.98 ± 1.36	82.74 ± 3.21	100 ± 0.50	0.488 ± 0.02	0.280 ± 0.01	33.72 ± 1.10	18.71 ± 0.82	0.686 ± 0.01	0.848 ± 0.005
4	98.35 ± 1.24	89.88 ± 1.32	79.90 ± 1.21	94.63 ± 1.56	1.018 ± 0.01	0.733 ± 0.01	34.90 ± 1.09	27.67 ± 0.80	0.486 ± 0.01	0.572 ± 0.007
5	93.56 ± 1.23	91.26 ± 1.41	86.37 ± 1.32	99.25 ± 1.37	0.583 ± 0.01	0.370 ± 0.01	38.45 ± 1.00	28.35 ± 0.91	0.665 ± 0.01	0.717 ± 0.005
6	89.63 ± 1.14	96.50 ± 1.33	86.20 ± 1.32	92.7 ± 1.58	0.555 ± 0.01	0.378 ± 0.01	25.49 ± 1.39	28.98 ± 0.95	0.682 ± 0.01	0.749 ± 0.02
7	95.62 ± 1.56	92.50 ± 1.20	81.16 ± 2.30	99.25 ± 1.09	1.198 ± 0.01	0.711 ± 0.01	36.51 ± 1.17	31.96 ± 1.00	0.451 ± 0.006	0.575 ± 0.02
8	89.50 ± 1.33	92.12 ± 2.00	83.27 ± 1.01	97.70 ± 1.54	0.859 ± 0.01	0.395 ± 0.01	30.21 ± 1.75	32.17 ± 1.00	0.539 ± 0.005	0.784 ± 0.04
9	88.00 ± 1.61	91.23 ± 0.65	89.26 ± 1.02	93.52 ± 1.07	0.413 ± 0.01	0.315 ± 0.01	31.59 ± 1.45	31.08 ± 1.05	0.733 ± 0.004	0.825 ± 0.03
A	–	–	–	–	1.992 ± 0.01		55.985 ± 0.92			

m: methanol, d: DCM, A: Accurel MP 1000.

drug content when polar methanol is used as solvent (data not shown).

3.2. Evaluation of drug-loaded microparticles

The molecular state of the adsorbed drug molecule was investigated by DSC and XRD studies. The DSC thermograms of the drug-loaded beads and polymer are shown in Fig. 1. Endothermic peaks were observed at 70 °C due to melting of drug and at 150 °C due to melting of crystalline polymer Accurel MP 1000®. The drug and Accurel MP 1000® displaying their characteristic individual melting trends without any appreciable deviation excepting a change in the energy levels, correlatable with the amount of drug loaded. Neither solvents nor melt adsorption changed the nature of drug. Stebule et al. (2004) had reported the change in the crystal habitat of the drug by using solvent evaporation for drug adsorption for theophylline. XRD in Fig. 2 also supports the results obtained by DSC. A diffraction pattern of polymer, drug and drug-loaded polymer are consistent in depicting the crystalline nature with difference in the intensities probably due to marginal effect of carrier interaction during adsorption. The FTIR in Fig. 3 indicates that the nature of interaction is a physical one rather than a chemical one for all drug adsorption processes studied.

Surface topography confirms the different patterns of the drug adsorption over the porous surface using selected variables

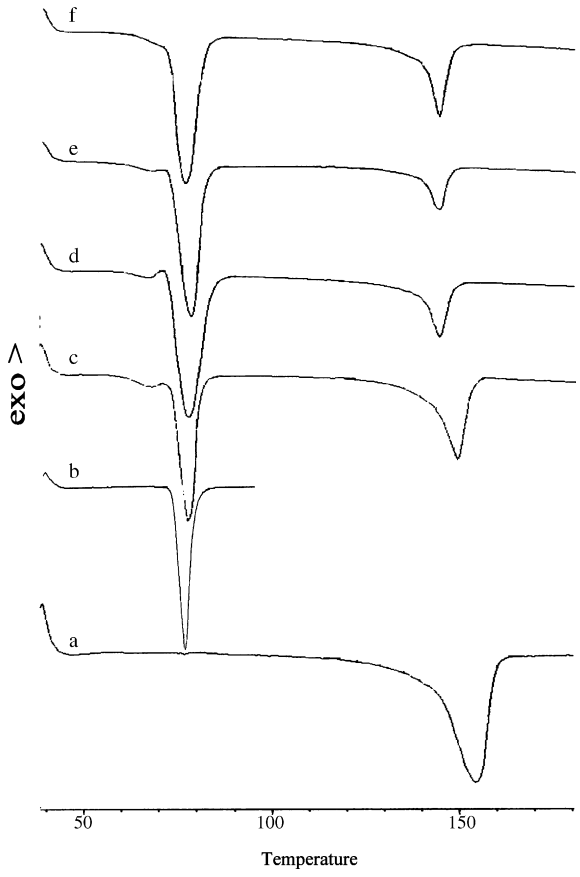

Fig. 1. DSC of (a) Accurel MP 1000 microparticles, (b) drug, (c) batch 4 methanol, (d) batch 4 DCM, (e) batch 2 methanol and (f) batch 3 DCM.

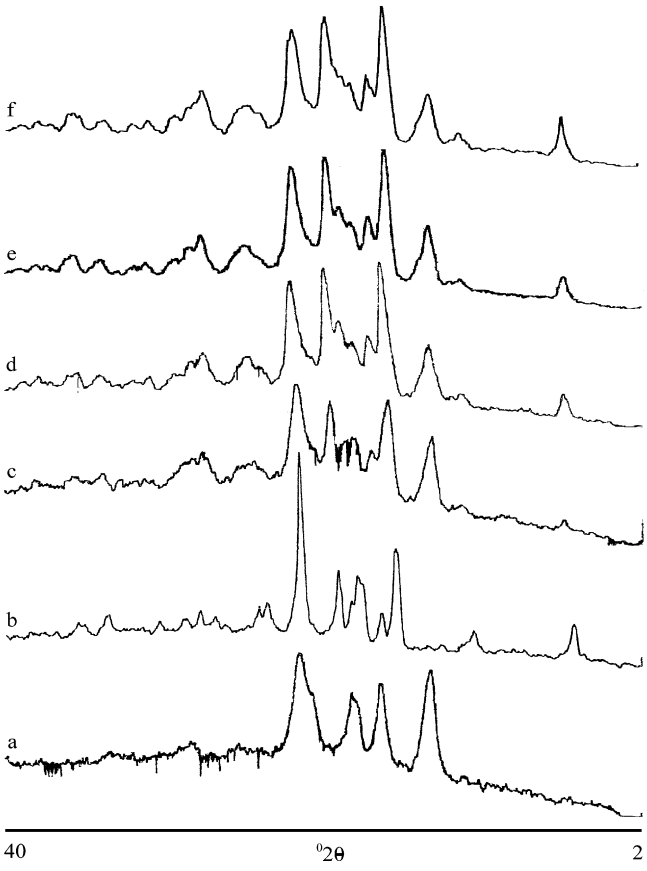

Fig. 2. XRD patterns of (a) Accurel MP 1000 microparticles, (b) drug, (c) batch 4 DCM, (d) batch 2 methanol, (e) batch 8 DCM and (f) batch 3 methanol.

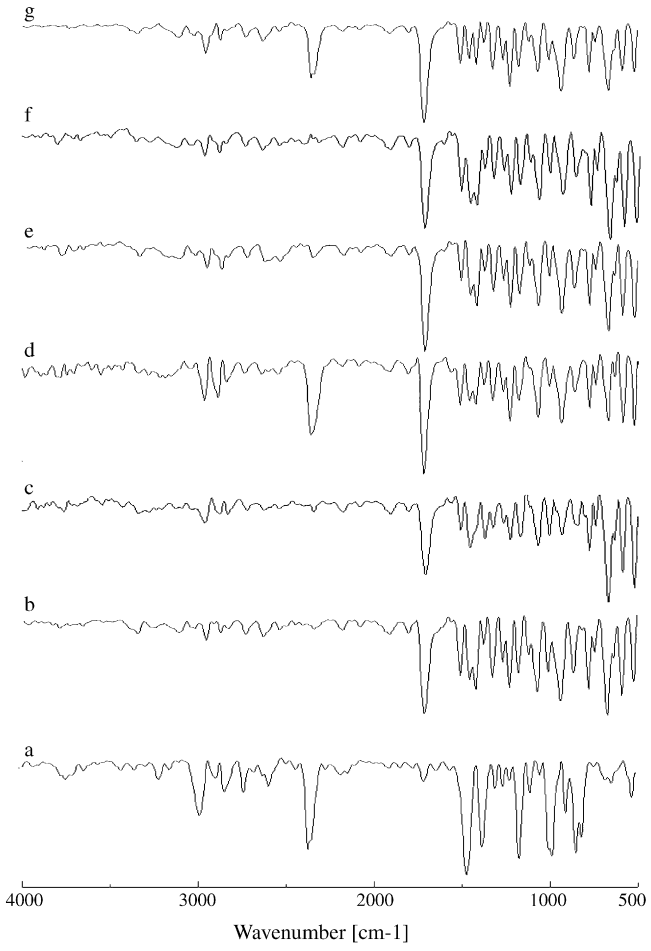

Fig. 3. FTIR spectra of (a) Accurel MP 1000 microparticles, (b) drug, (c) batch 3 DCM, (d) batch 7 DCM, (e) batch 5 methanol, (f) batch 6 DCM and (g) batch 9 methanol.

as seen in Fig. 4. Methanol seems to facilitate migration of drug molecules into the pores of the Accurel MP 1000 microparticles® as in Fig. 4 due to lower viscosity and slow phase transformation. This also shows the interactive and transport behavior of drug, in polar methanol over hydrophobic polypropylene surface, having both hydrophilic and hydrophobic segment, where as polar interactions take place between adsorbed molecules of methanol and those in the solution. The magnitude of this reaction depends upon free energy of solid and the dispersed adsorbate (Janczuk et al., 1985). DCM relative to methanol has low boiling point indicating fast phase change. With DCM as solvent, the migration of the drug molecules using DCM seem to be restricted mostly to pores near the surface, leading to the formation of stakes. This can be assumed to be the effect of the inherent physical characteristics of DCM influencing the adsorption pattern on and within porous network of the polymer. It has been indicated that evaporation takes place from the hemispherical menisci at each end of the cylindrical pore (Sarkisov and Monson, 2001). TGA studies point to surface adsorption pattern on the surface which can be suggested by the results as seen in Fig. 5. The weight loss pattern follows the same trajectory as that of drug alone, totally independent from that of polymer.

Drying of solvent containing drug, lead to adsorption pattern at different areas which depend upon geometry, size, and configuration of porous network. The aggregation of adsorbate in a pore network gives rise to continuous and discontinuous clusters governing pore volume and pore size of the porous material. MPA was done to evaluate the porous structure before and after drug loading. All the isotherms followed type III pattern. The pore volume of Accurel MP 1000® was 1.992 cm^3/g and surface area was 55.985 m^2/g. Drug adsorption varied using solvents due to their characteristic boiling points, polar characters and dielectric constants. Ibuprofen contain a polar group –COOH and a non-polar group $–CH(CH_3)C_6H_4CH_2CH(CH_3)_2$. The adsorption of ibuprofen show distinct behavior on hydrophobic layer in which they appear as dimmers having a twisted 3d structure, although the adsorption of the dimmers in the pores with $\geq$1 nm is entirely possible. Pore size distribution in Accurel MP 1000, having micro as well as macropores can absorb both monomers and dimmers of the ibuprofen (Gunko et al., 2004). Pore volume decreased with increasing drug amount and subsequently increased by increasing solvent volume using methanol. Capillarity gradients vanish at complete solvent saturation/submerging of adsorbent, thereby, depending on the boundary conditions, pressure gradients may replace them (Germann and DiPietro, 1996). Thus, at 3 and 5 mL of methanol, the pressure gradient helped the drug to migrate deep inside the pores in turn reducing the aggregation at the surface,

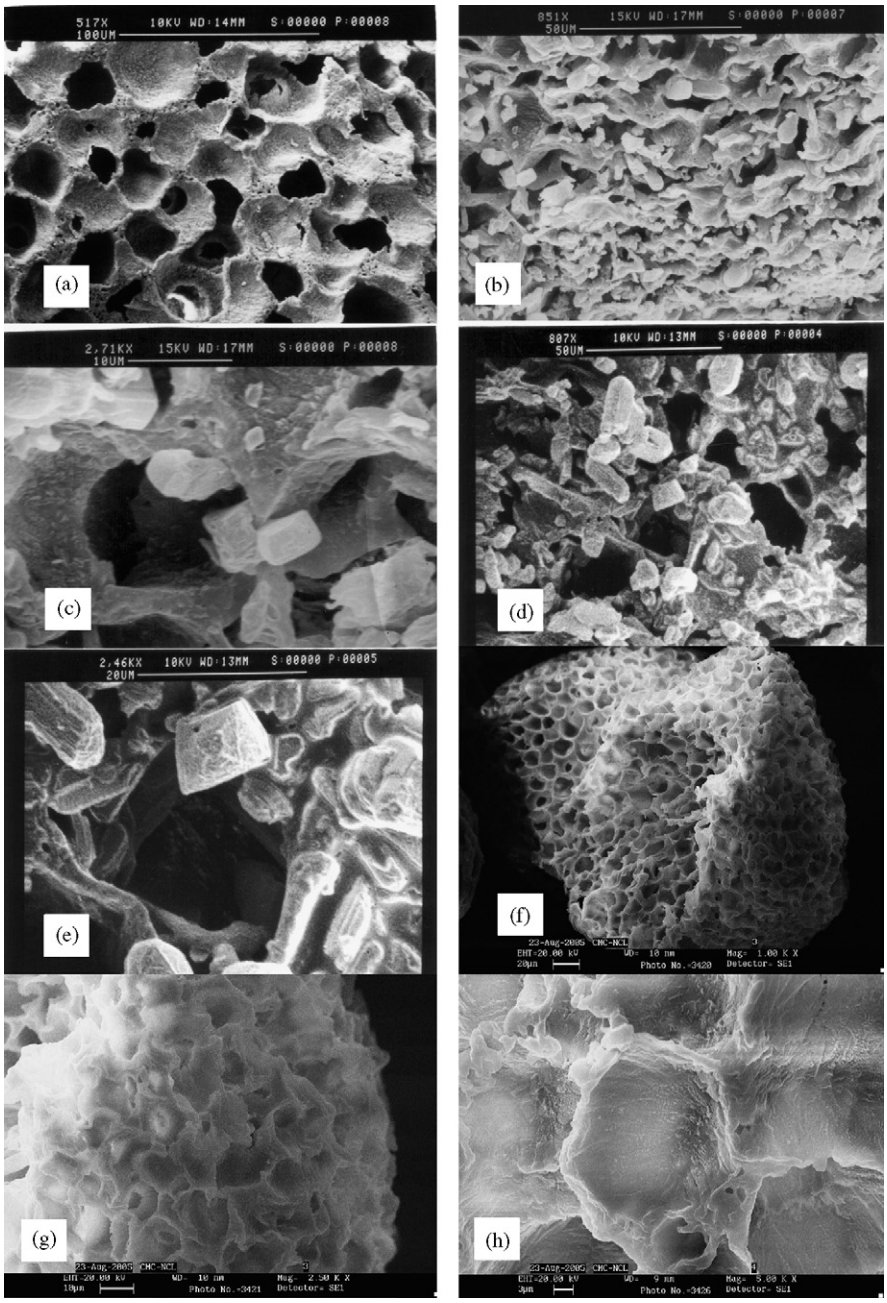

Fig. 4. SEM of (a) Accurel MP 1000 microparticles, (b and c) batch 9 methanol, (d and e) batch 6 methanol, (f and g) batch 4 DCM and (h) batch 9 DCM.

causing an increase in the pore volume, with the exception of batch 9 where large amount of drug must have developed multiple clusters. This migration can be due to the synergistic effect of interaction of the polar methanol with the hydrophobic surface and volume of solvent causing discreet adsorption pattern.

For DCM, the values of pore volume and surface area are less relative to methanol as in Table 2. The lower pore volume and low intra range of the surface area within the batches indicate the blocked pores caused by the staking of the drug over the surface. These influences arise due to less polar nature and low boiling point of DCM on hydrophobic surface causing difference in drug adsorption, evident from the SEM. The effects on bulk density is given in Table 2. Bulk density decreased as the solvent volume increases with each different drug loading. Over all, pore volume decreased with increasing amount of drug irrespective of solvent volume and type used. This shows the increase in the surface adsorption and underlying pores with increasing drug amount. With lowest amount of drug, changing volumes of solvent led to increase in pore volume due to the change of capillary effect to pressure gradient. This effect was nullified with increasing drug amount which might have filled the pores irrespective of volume of solvent used.

Statistically interpreting the data by regression analysis, the values for drug amount (X_2) predict negative influence over pore volume (Fig. 6a and b) than volume (X_1) of both solvents as in Table 3. This negative influence can be related to the deposition

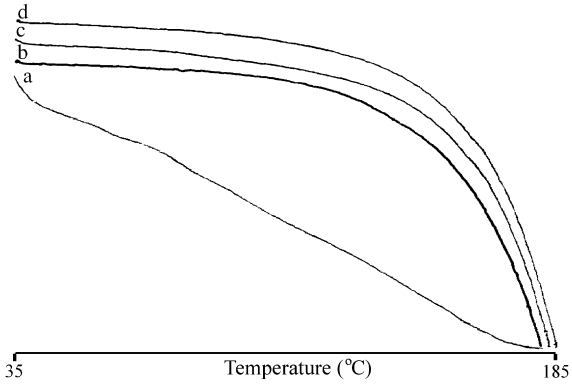

Fig. 5. TGA of (a) Accurel MP 1000 microparticles, (b) drug, (c) batch 9 DCM and (d) batch 9 methanol.

of the drug on surface pore boundaries. The influence of the nature of solvent on surface area is clearly observed (Fig. 6c). DCM shows negative value for drug amount, positive value for solvent volume and interaction with other variables. Methanol show prominent influence of drug amount (X_2). Less polar and low dielectric constant nature of DCM is reflected in influencing the surface area characteristic of Accurel MP 1000® than that of methanol.

3.3. In vitro drug release

In vitro dissolution was studied for 6 h in pH 7.2 phosphate buffer IP. Drug release was not linear for all batches with recovery up to 25%. With methanol as solvent for drug adsorption, the drug release was in the range 45–92% and for DCM it varied from 82 to 100%. The drug release pattern show distinct characteristic termed as "triphasic", in which an initial rapid drug release is refereed as "burst effect" followed by much slower drug release and then finally a cut off or tapered phase where, either the cumulative drug release stops earlier with recovery or releases completely. The burst release corresponds to the release of the drug adsorbed over the surface and from pore network that is connected to surface. The later slow phase is due to diffusion of the drug through the network of pores lying inside, which is governed by the concentration and pore geometries filed with aqueous medium. During dissolution it can be assumed that interconnected pores allowing fluid flow causing mass trans-

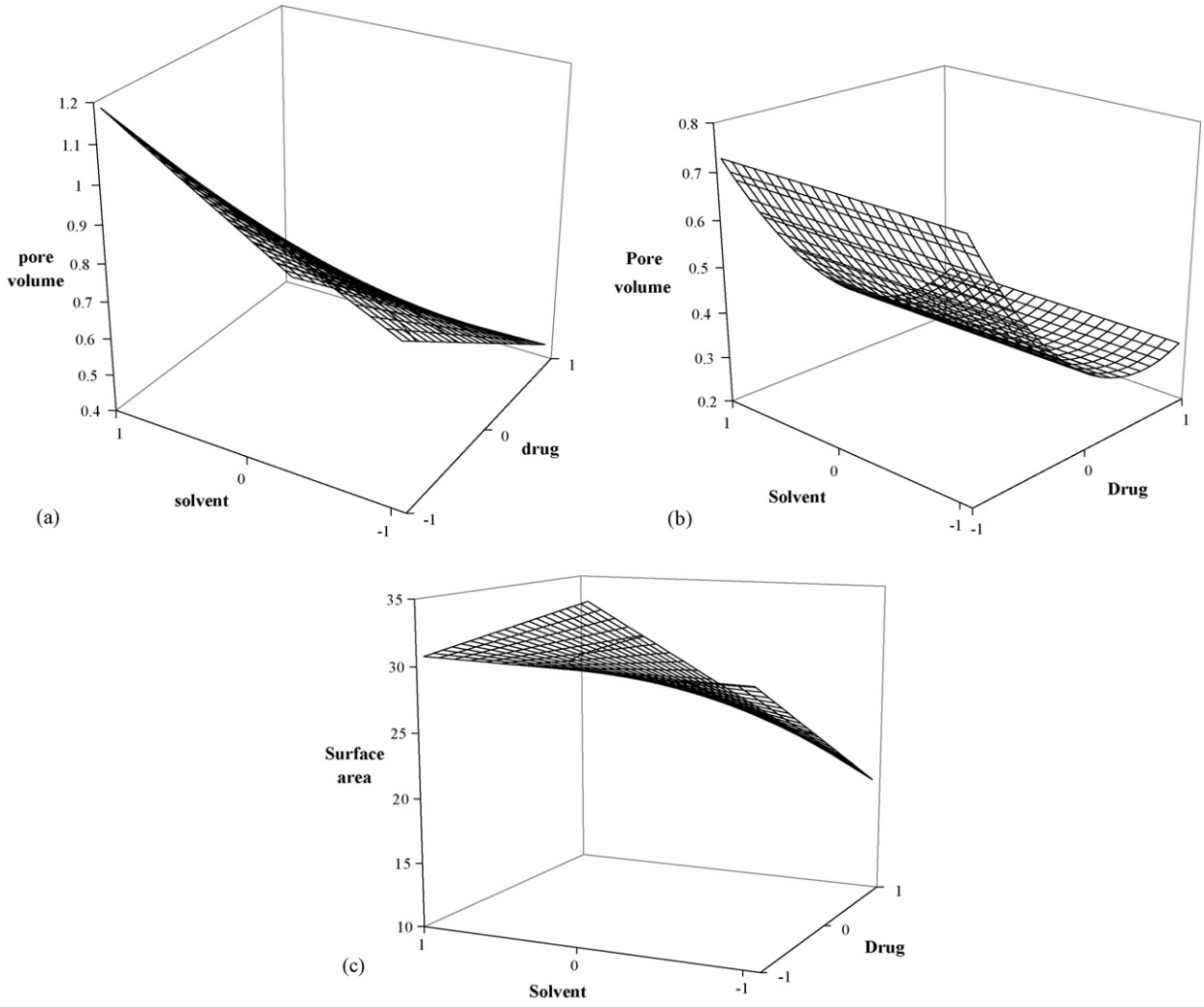

Fig. 6. Response surface plot showing effect of factorial variables on (a) pore volume (methanol), (b) pore volume (DCM) and (c) surface area (DCM).

Table 3
Estimation of regression coefficients for different response variables

Coefficient	Responses											
	Bulk density		Pore volume		Surface area		Release at 60 min (%)		Release at 120 min (%)		Release at 180 min (%)	
	m	d	m	d	m	d	m	d	m	d	m	d
C	0.597	0.700	0.719	0.366	33.224	28.199	86.56	85.836	83.33	94.45	86.27	98.50
α	0.108	0.119	0.086	–	–	3.6125	−14.53	–	−11.82	–	−12.05	–
β	–	–	−0.292	−0.204	−2.845	–	–	–	–	6.693	–	6.433
α^2	–	–	–	–	–	–	−15.22	–	−11.98	–	−14.48	–
β^2	–	–	–	0.162	–	−2.240	−7.03	−9.266	–	−13.09	–	−15.31
$\alpha\beta$	–	–	−0.094	–	–	3.2485	9.052	9.142	11.772	7.995	11.64	8.85
R^2	0.851	0.8585	0.9457	0.9748	0.3864	0.8193	0.9635	0.7781	0.9409	0.9035	0.9530	0.9461
Sig.	0.0004	0.0003	0.0014	0.001	0.0139	0.0264	0.0039	0.0119	0.0017	0.0057	0.0010	0.0013

(–): Not in a function.

fer constitute for the contributing porosity. The remaining pores which are physically isolated form non-contributing pores. The permeability factor can be responsible for causing change in the drug release. The fluid paths continuously change adopting the least resistant channels (Civan Faruk, 2001). Similar cut off or recovery phenomenon had been observed; in macroporous polymers were at low drug loading the drug molecules appears to be trapped inside the matrix never to be released due to sparsely dispersed drug molecule through the porous network (Siegel et al., 1990; Siegel and Langer, 1990). Transport of adsorbate governed by diffusion depends on pore fluid volume. Restricted pore diffusion due to medium interaction with the surface, vary with loading due to influence of void fraction in porous adsorbent particles and pore diffusion coefficient of adsorbate (Tongta et al., 1994). Other related factors governing this phase are impermeability of the dissolution medium and low diffusitivities due to polypropylene.

3.3.1. Drug release from microparticles using methanol for drug adsorption

Methanol with high boiling point, high dielectric constant and polar nature tend to show prolonged slow release after a burst release with recovery. It has been theorized that multiple mechanism causing mass transfer and large tortuosity values depending

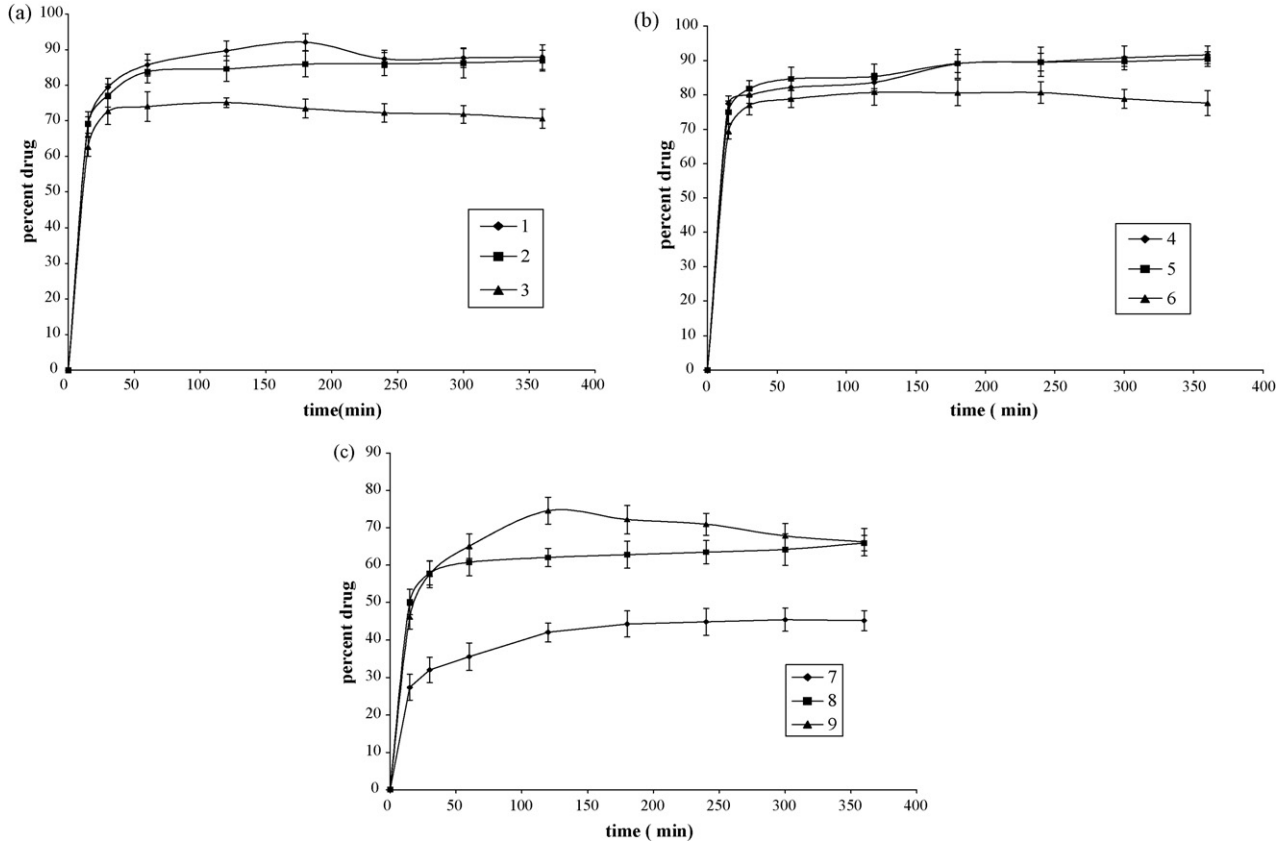

Fig. 7. Cumulative drug release profile from Accurel MP 1000 using methanol: (a) batch 1–3, (b) batch 4–6 and (c) batch 7–9.

on pore network may exist in porous material exhibiting large retardations in release. Depending on the drug loading, the resultant porous network can exist as large pores connected by small channels. In addition to pore geometry and steric considerations, physical and chemical interactions, partitioning of the diffusant with the matrix walls also retarded release (Scott, 2001).

Batches 1, 2 and 3, 5 using 1 mL methanol, drug release ranged 75–92% with continuous release for the batch 2 (Fig. 7a). At low volume of methanol capillary effect is pronounced than pressure gradient. This leads drug to prominently adsorb on the surface and underlining pore network forming continuous clusters, therby, providing fast release. Also, at low level of drug amount the surface effect is also prominent for increasing the drug release. In these batches relative contribution of adsorption on surface and in pores occurs simultaneously there by eliminating the possible impact of the single process. Burst release, without much variation was least for batch 3, due to low pore volume and total intruded volume. The quantum of release in slow phase decreases with increasing drug amounts due to decrease in exposed surface area for mass transfer. This is followed by cut off at 3 and 2 h for batches 1 and 3, respectively, subsequently showing recovery. As the dissolution proceeds, depletion of drug on surface and underlying pore forming continuous layer expose the hydrophobic porous surface inhibiting drug release, thereby, leading to recovery. Batches 4, 5 and 6, using 3 mL methanol, drug release ranged from 80 to 91% with continuous release for batches 4 and 5 (Fig. 7b). The burst and cumulative release was slightly higher. The capillary as well as pressure gradient seem to work collectively to impart positive influence of solvent volume on drug adsorption. The pattern of adsorbed drug showed increased continuity, thereby, have high contributing porosity. The quantum of drug release after burst release is slow and less than using 1 mL solvent. Recovery about 20% is observed in batch 6 only. In this batch relative contribution of adsorption on surface and in pores occurs differently due to high amount of drug causing multiple adsorption fronts. In batches 7, 8 and 9 the drug release ranged 45–74% with continuous release for batch 8 only, using 5 mL methanol (Fig. 7c). The burst and total release was least. The solvent volume shows prominent pressure gradient effect. This is exactly opposite using least, 1 mL, solvent volume where capillary forces dominate. The burst release is least for batch 7, which otherwise is maximum with other solvent volumes for same amount of drug. The high volume of solvent, leading to deep penetration of drug seems to nullify the effect of surface area. The same effect is observed in batch 8 and 9. The quantum of drug release in slow phase was least. Maximum release was observed for batch 9 having high level of drug (300 mg), irrespective of 25% recovery. The cumulative drug release showed opposite trend than using other solvent volumes, where, least amount of drug (100 mg) showed maximum drug release. Batch 7 almost showed linear release during experiment time having a cut off at 5 h. The change in volume definitely has shown difference in the drug release properties. Batches 2, 5 and 8, having the polymer:drug ratio

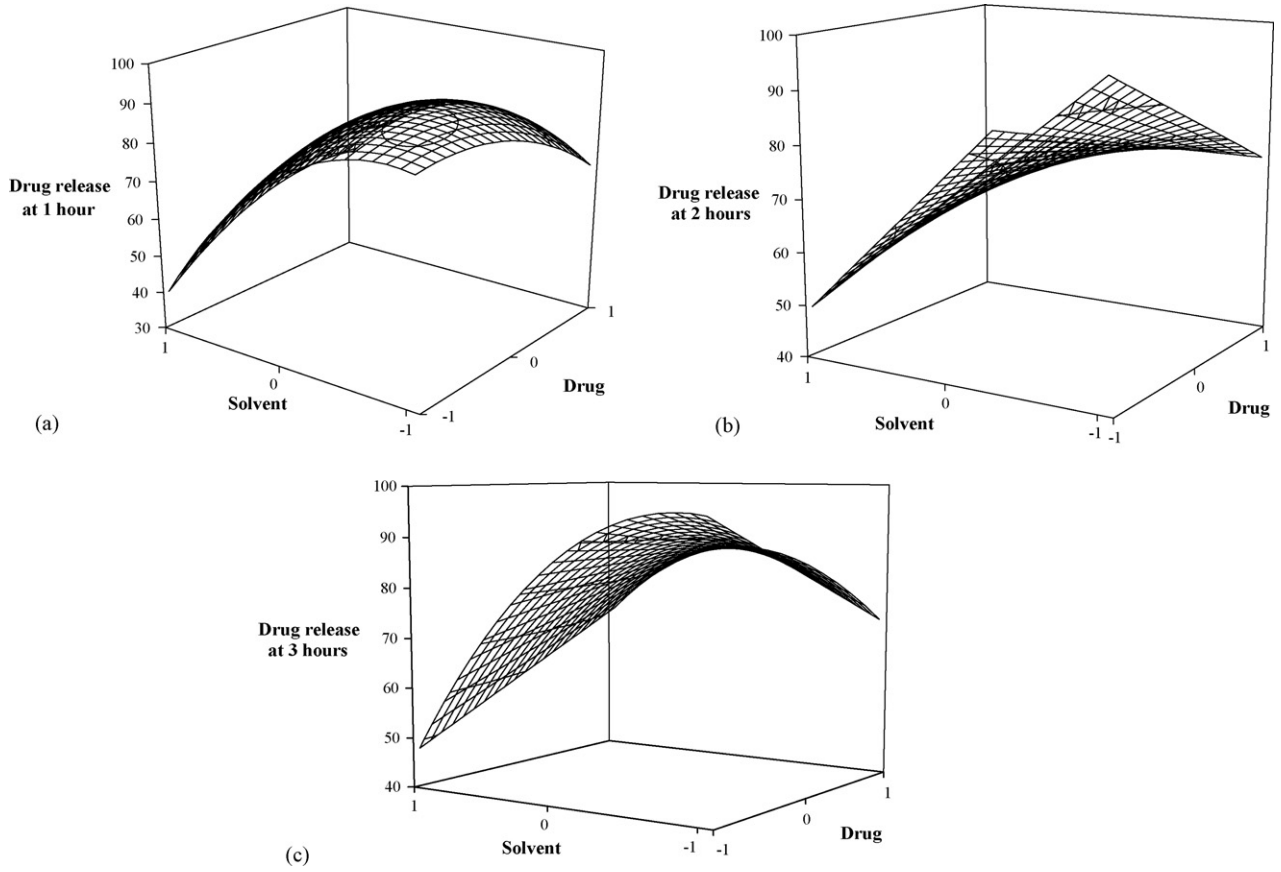

Fig. 8. Response surface plot showing effect of factorial variables on drug release at: (a) 1 h, (b) 2 h and (c) 3 h.

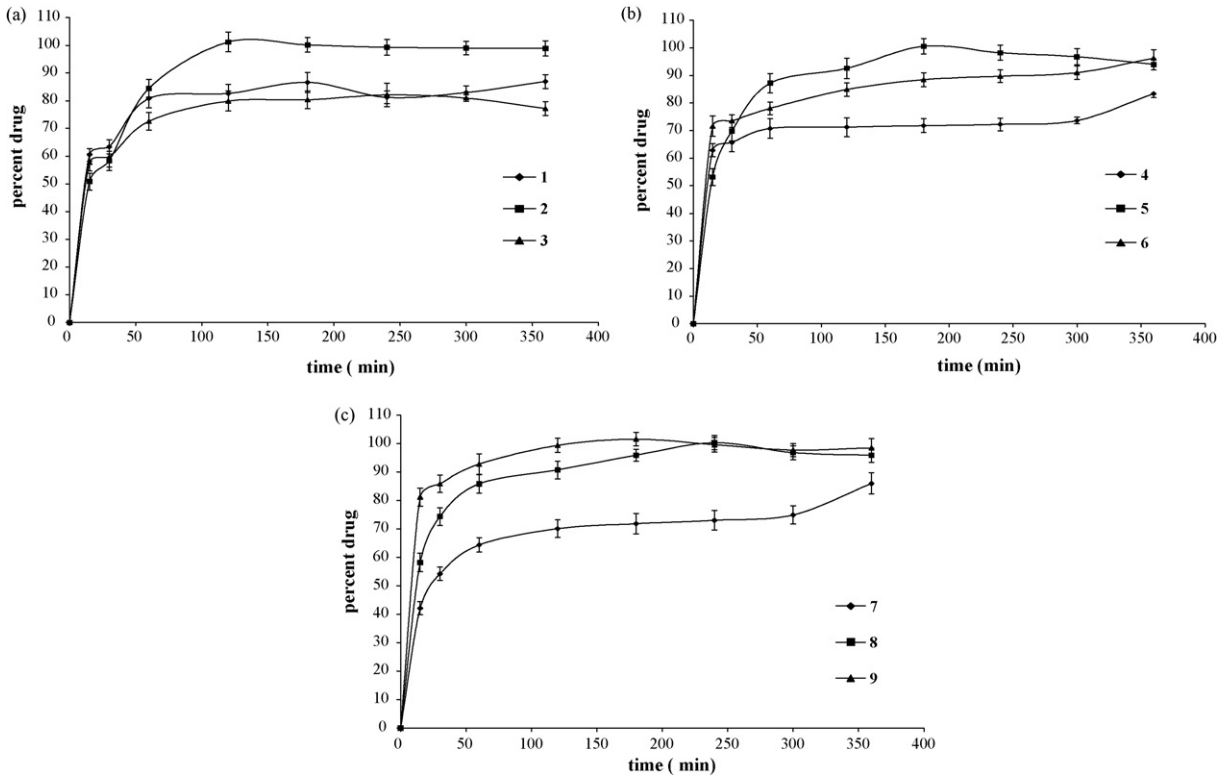

Fig. 9. Cumulative drug release profile from Accurel MP 1000 using DCM: (a) batch 1–3, (b) batch 4–6 and (c) batch 7–9.

of 1:2, is devoid of cut off regardless of the solvent volume used.

Statistical interpretations calculated for the amount of drug release at 60, 120 and 180 min (Fig. 8a–c) were preferred over the percent release to nullify the effect of recovery or cut off along with burst release. The values conferred the negative impact of the both solvent and drug and the positive impact of their interaction on drug release as in Table 3. The impact of the solvent variable seems to increase as the time increases. The effect of solvent on drug adsorption seems to play a crucial role which can be interpreted by the positive interaction values influencing drug release. The contribution of both variables shows a definite effect on release pattern therby singling out any one variable.

3.3.2. Drug release from microparticles using DCM for drug adsorption

The drug release using DCM was in the range of 82–100%. With DCM having low boiling point, low dielectric constant and less polar nature than methanol tend to have different adsorption geometry at the surface in the form of dimmers. Fast transformation of the phases due to low boiling point, low dielectric constant, polarity difference and hydrophobic property of the adsorbent surface increase adsorption at the pore ends due to capillary condensation as observed in SEM also. The drug release using DCM showed complete release for some batches relative to methanol.

Batches 1, 2 and 3 using 1 mL DCM, drug release ranged 82–100% with batch 2 showing complete release in 2 h (Fig. 9a). Batch 2 also show less burst release followed by high quantum release as compared to other two batches. This relates to different adsorption pattern having continuous clusters of adsorbed drug on the surface limiting very little to pores due to the influence of solvent properties. Also using 1 mL DCM, capillary action must have resorted to the maximum adsorption at the surface. In batch 3, high drug amount led to the packing of the surface and pores therby showing continuous release till 4 h. Batch 1, with low drug amount show maximum burst release followed by slow release and a cut off at 3 h. The increased pore volume assisted by high surface area must have contributed to this release pattern. The high burst release also expose the under lying hydrophobic surface which contribute in retarding the release followed by recovery. Comparing with batches using methanol, batch 2 showed the maximum difference with complete release. Batches 4, 5 and 6 using 3 mL DCM, drug release ranged 83–100% with batch 5 showing complete release (Fig. 9b). The burst release and the cumulative drug release increased mirroring while using same methanol volume. The increased adsorption of the drug on the surface must have provided the source for high burst release. Batch 5 show least burst effect, whereas, complete release was delayed by 1 h as compared to batch 2 having same amount of drug. This shows the best synergistic effect of capillary with pressure gradient due to increased volume of solvent where the adsorbed drug clusters seems to be pushed further inside. Batches 4 and 6, showed linear drug release for stipulated experimental time. The number of contributing clusters seems to increase suggesting increased drug release from batch 6 near complete, when compared with batch 3 having same amount of drug. Relative to methanol, major difference is the batch 5 having complete drug release. Batches 7, 8 and 9 depict drug release range 86–100%, with batch 8 and 9 having complete release

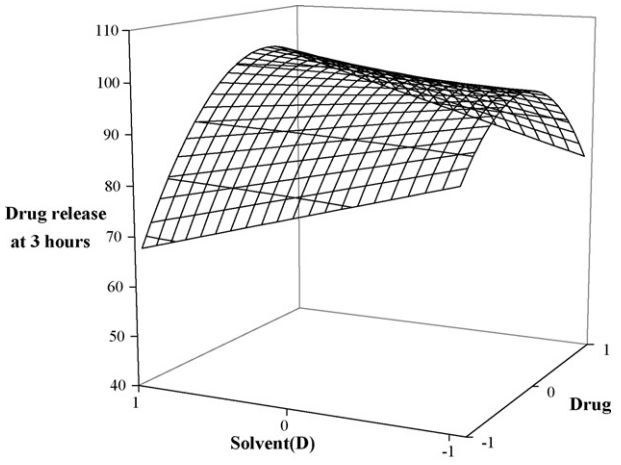

Fig. 10. Response surface plot showing effect of factorial variables on drug release at 3 h using DCM.

using 5 mL DCM. Burst release increased with the increasing amount of drug which altered the trend for last two volumes of solvent used. The impact of the pressure gradient is quite evident in these batches. Batch 8, shows complete drug release with delay of 1 h when compared with batch 5 having same amount of drug (200 mg). The quantum of drug release seem to decrease in batches 7 and 8 containing 100 and 200 mg drug, respectively, while as trend reverses in batch 9 having 300 mg drug corresponding to that batches with same amount of drug. Comparing with methanol, the drug release is on higher side along with batch 8 and 9 having complete drug release. The cumulative release using maximum amount of drug (300 mg), increased with increasing solvent volume which is opposite while using methanol.

Batch 2, 5, 8 having same amount of drug (200 mg), showed complete drug release irrespective of solvent volume used for adsorption. Overall polymer: drug ratio of 1:2 seems to show particular characteristics in both the solvents.

Statistical interpretations calculated for the amount of drug release at 60, 120 and 180 min interpret the effective influence of the amount of the drug and its interaction with the solvent (Fig. 10). The positive sign of the interaction of drug and solvent govern the adsorption of the drug effect on drug release which is also favored by the drug–drug interaction as the time progresses. Amount of drug is the crucial for the drug release along with interaction with solvent.

4. Conclusion

The assumption for the mass transfer leading to the drug release from the porous material can be correlated with the moment of the dissolution medium inside the porous network, drug diffusion within the porous network, drug diffusion through the unstirred liquid boundary layer on the surface, flow of diffused drug into medium and the pattern of the drug adsorbed on and inside the pore network. Volume of solvent shows its influence in retarding the drug release depending upon the drug amount and its nature. The irregular pattern of drug adsorption was noticed using methanol contrary to use of DCM. Polarity effect on hydrophobic materials with or with any surface modification alters the drug release.

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