Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2010; 2(2) 26-34

ISSN: 0975 4415

Research Article

Use of Microporous Accurel MP1000 for Duodenal Delivery of Secnidazole: A High Dose, Gastric pH Unstable Drug

Amit Singh, Deepa Pathak, Kamla Pathak*

Department of Pharmaceutics, Rajiv Academy for Pharmacy, National Highway-2 P.O. Chhattikara, Mathura, Uttar Pradesh, India, 28100

ABSTRACT

Secnidazole, a high dose antiprotozoal agent unstable at gastric pH was used as a model compound for deposition onto the adsorbent carriers by two methods namely solvent deposition and physical mixing for duodenal delivery. The drug/adsorbent systems were evaluated for pharmacotechnical properties and characterized by FT-IR, DSC, XRD, SEM and in vitro dissolution testing to investigate the influence of carriers and methods of preparation on in vitro drug release. The solvent deposited secnidazole adsorbates (F4-F6) with high drug loading capacity and better control on dissolution at all time points were subjected to modified release by encapsulating in formaldehyde treated PVP K40 coated capsules. The optimized formulation was able to maintain zero order release with a maximum release of 95.91% at the end of 8 h in contrast to marketed formulation that gave a burst release of 67.89% within 2.5 hours followed by a non zero order release of 87.89% at the end of fifth hour. Thus a formulation of secnidazole accurel adsorbates could be developed that when suitably designed provided controlled duodenal delivery.

Keywords: Secnidazole, Accurel MP 1000, in vitro adsorption , PVP K40 coated capsule, duodenal delivery

INTRODUCTION

Controlled drug delivery systems offer advantages over conventional dosage forms, in terms of enhanced efficiency of medicine, improved patient compliance and convenience to patients (Sher et al 2007). The method by which a drug is delivered can have a significant effect on its therapeutic efficacy that is in turn dependent on dissolution of drug. Reduction of the particle size/increase in the surface area of the drug is a widely used and relatively simple method for increasing dissolution rates, but often results in agglomeration of particles thereby affecting dissolution. Of the many approaches researched for controlled drug delivery systems use of adsorbents (Chang et al 2006; Zhang et al 1994) appears particularly suited for controlled release and drug targeting (Benita 1996; Charnay et al 2004).The incorporation of drug into carriers or deposition onto adsorbents (Ito et al 2005; Alsaidan et al 1998) tends to reduce the tendency of the drug agglomeration and thereby increase the dissolution rate. The surface area of the drug available for contact with the dissolution medium is increased by the use of particulate adsorbents carriers, whereby the drug is bound to the carriers and thus cannot agglomerate. Large number of adsorbents is reported in literature for variety of purposes. Synthetic adsorbents are widely used as polymeric media for recovery and separation of pharmaceuticals or their intermediates, foods, nutraceuticals, etc. and for separation of antibiotics such as penicillin, cephalosporin and their derivatives. The adsorbents because of their high adsorption capacity, mechanical strength and chemical stability are suitable for industrial operations (Adichi et al 2004).

Address for correspondence :Kamla Pathak
Department of Pharmaceutics
Rajiv Academy for Pharmacy, NH #2
P.O. Chhattikara, Mathura,
Uttar Pradesh (INDIA) 281001
Email:kamla_rap@yahoo.co.in;
kamlapathak5@gmail.com

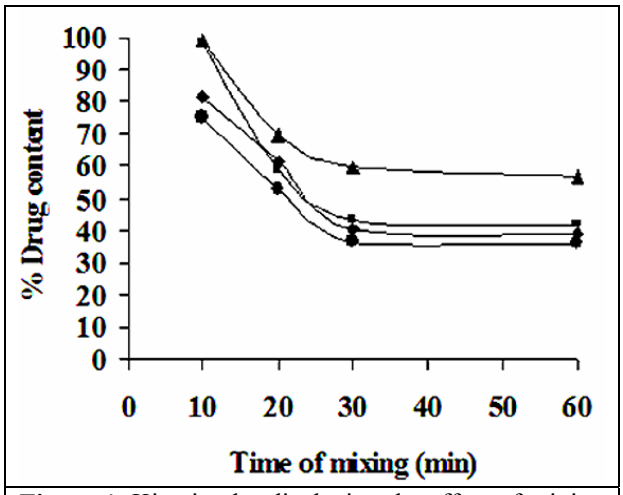

Figure 1. Kinetic plot displaying the effect of mixing time on the adsorption of secnidazole on sifted fractions of accurel MP 1000 (-♦-) # 85-100 ; (-■-) #100-120; (-▲-) 120 -180; (-●-) < #180

A relatively newer group of porous carriers that are low-density solids with open or closed pore structure and provide large exposed surface area have been used for drug loading. Their hydrophobicity varies from completely hydrophilic carriers, which immediately disperse or dissolve in water, to completely hydrophobic

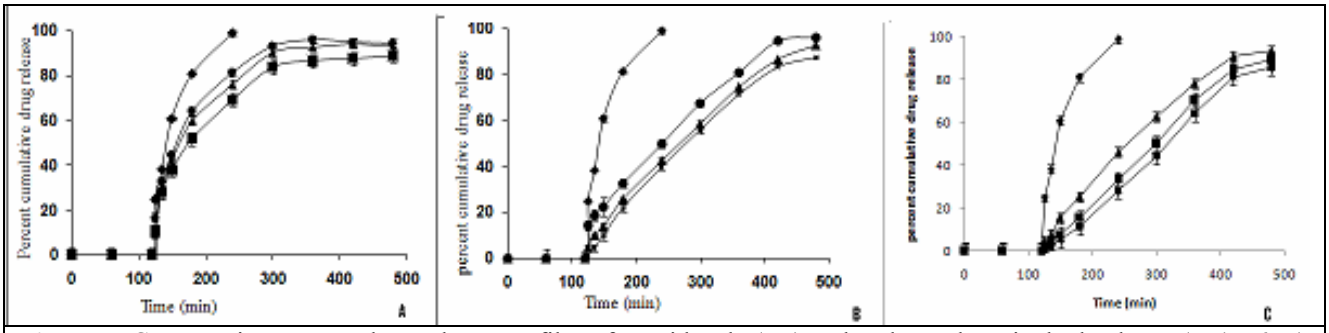

Figure 2. Comparative percent drug release profiles of secnidazole (-♦-) and solvent deposited adsorbates (-■-) F6; (-▲-) F4; (-●-) F5 filled in (A) 2.5 % w/v polymer coated ; (B) 5 % w/v polymer coated and (C) 7.5 % w/v polymer coated formaldehyde treated capsule

ones, which float on water for hours. Owing to a wide range of useful properties, porous carriers have been used in pharmaceuticals for many purposes including development of novel drug delivery systems such as floating drug delivery systems and sustained drug delivery systems, improvement of solubility of poorly water soluble drug and enzyme immobilization (Sharma et al 2005; Salis et al 2003; Yuasa et al 1996; Struebel et al 2002; Streubel et al 2003). Microporous adsorption polymers developed during the last years are characterized by very little pore diameters and high specific surface area (1400m^2/g). Their adsorption capacities are two to five times higher than that of macroporous ones, and can be useful carriers for loading of high dose drugs(Friedrich et al 2006; Zheng et al 2007; Masque et al 1999). Much of this work involves polymers to enable the drug to be delivered at relatively constant rate by diffusion control from polymer or polymer composites over a period of time (Li et al 2001; Shen et al 2007).

Table 1. Solubility data of secnidazole in various pH at variable time intervals.

S. No	Phosphate buffer, pH	Solubility (mg/ml)		
		After 24 h	After 48 h	After 72 h
1	4.0	46.62 ± 0.35	49.02 ± 0.18	49.88 ± 0.15
2	6.8	44.08 ± 0.18	46.54 ± 0.12	47.72 ± 0.16
3	7.4	37.68 ± 0.15	39.48 ± 0.19	41.06 ± 0.15
4	9.0	35.02 ± 0.09	37.16 ± 0.12	38.68 ± 0.19

The adsorbates of a drug with a carrier can be formed by precipitation of both species from a common solvent and drug can also be deposited from a volatile solvent onto a solid surface, a technique termed as solvent deposition. The solvent deposition method is readily adaptable for thermolabile drugs and carriers many polymers with high melting temperatures that cannot be utilized in other processes could be carriers for solvent deposited drug formulations. This is accomplished by dissolving the drug in an organic solvent and adsorbing this solution onto the carriers. The evaporation of the organic solvent results in a rapid precipitation of the drug either on the surface or within pores of the adsorbent material (Davis et al 2002). Alsaidan et al. (1998) have reported improved dissolution rates of indomethacin adsorbed onto the surfaces of adsorbents. Moreover, simple blends of the drug with the carriers have also been reported to increase dissolution rates though to a lesser extent (Williams et al 2005).

Secnidazole [1-(2-hydroxypropyl)-2-methyl-5-nitroimidazole], a high dose (single dose of 2g in adult or 30mg/kg body weight in children) antiprotozoal agent (Brar 2000) that is unstable at gastric pH was used as a model compound for deposition onto the adsorbent carriers by two methods namely solvent deposition and physical mix. The drug/adsorbent systems were characterized by FT-IR spectroscopy, Differential scanning calorimetry (DSC), X-ray powder Diffractrometry (XRD), Scanning electron microscopy (SEM) and dissolution testing to investigate the influence of carriers and methods of preparation on in drug release. Secondly to develop a formulation capable of delivery the drug beyond duodenum in a controlled release manner.

MATERIALS AND METHODS

Materials

Secnidazole (SDZ) was kindly provided by Aarti Drugs Ltd., Mumbai, Aerosil-200 from S Merck (India) Limited, Bentonite from s.d. Fine Chem Limited, Mumbai, Kaolin from S Merck (India) Limited, Microcrystalline cellulose from s.d. Fine Chem Limited, Mumbai, Silica gel-G from Thomas Baker (Chemicals) Limited, Mumbai and Accurel-MP1000 was procured from Membrana GmbH, Accurel Systems, Obernburg, Germany.

Solubility studies

Solubility of bulk drug was determined from equilibrated suspensions of the drug in phosphate buffers of varying pH values (4.0, 6.8, 7.4 and 9.0). An excess amount of drug was added to 10ml of solubility media separately and shaken in water bath shaker (Hicon Enterprises, India) at 37± 0.5° C. At various time intervals (24, 48 and 72 hr) the samples were withdrawn filtered through Millipore filters (0.45 µ) and analyzed spectrophotometrically (Shimadzu Pharma spec 1700, Japan) at 319 nm. The solubility values were determined from the calibration curve. An average of three replicates was taken.

Characterization of Adsorbents

Particle size and particle size distribution

Particle size of the adsorbents were determined using Malvern zeta sizer (Model No. 3000 HF, Malvern

Table 2. Physical and micromeritic characteristics of the adsorbates screened for preparation of secnidazole adsorbates.

Adsorbent	Z	PDI	Cfu	Bulk density g/cc	True density g/cc	Tapped density g/cc	Hausner 's ratio	Porosity (%)	Flow property	% drug adsorbed
Aerosil-200	830.2 ±1.75	0.66 ±0.04	0.900 ±0.12	0.03 ±0.01	0.26 ±0.04	0.054 ±0.07	1.54 ±0.24	81.15 ±1.94	poor	86.67 ±1.33
Accurel MP1000	347.2 ±1.44	1.000 ±0.06	1.521 ±0.12	0.23 ±0.04	1.30 ±0.17	0.129 ±0.06	0.549 ±0.02	86.85 ±1.27	excellent	88.62 ±2.01
Bentonite	1049 ±1.04	0.606 ±0.02	0.791 ±0.16	0.80 ±0.44	2.59 ±0.35	0.635 ±0.07	0.794 ±0.12	69.11 ±2.36	excellent	74.33 ±1.84
Kaolin	2546 ±2.09	0.272 ±0.05	0.886 ±0.11	0.78 ±0.14	2.51 ±0.21	0.469 ±0.09	0.601 ±0.08	67.09 ±1.14	excellent	75.97 ±2.08
MCC	3701 ±3.37	1.000 ±0.02	0.950 ±0.17	0.33 ±0.04	1.55 ±0.12	0.430 ±0.06	1.28 ±0.27	78.81 ±1.04	poor	82.19 ±1.98
Silicagel-G	5447 ±3.35	1.000 ±0.03	0.739 ±0.19	0.88 ±0.16	2.64 ±0.33	0.399 ±0.01	0.453 ±0.09	66.67 ±2.08	excellent	73.31 ±2.94

instrument Ltd, Malvern, UK) using water as the dispersant media.

Density determinations

An approximated quantity of adsorbents was put into a 100 ml graduated cylinder up to 50 c.c mark. The cylinder was then weighed to know the mass of the added bulk powder. The apparent bulk density was calculated from the volume occupied by the solid. The bulk adsorbent was submitted to three series of percussions (1 inch) using Tapped Density apparatus (Hicon Enterprises, New Delhi, India). The tapped density was determined from the final volume. The true density of the adsorbent was determined by liquid displacement method using ethanol (95%v/v) as the displacing liquid. The true density and bulk density determinations were used to determine Hausner's index and porosity (Martin 1999).

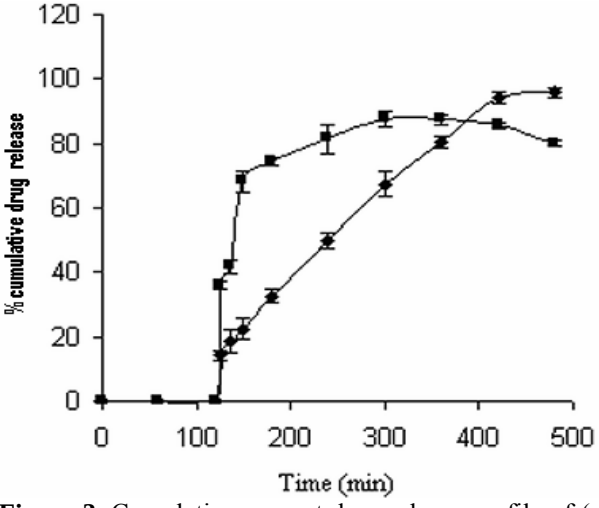

Figure 3. Cumulative percent drug release profile of (-■-) marketed versus (-♦-) optimized formulation F4 of secnidazole

In-vitro adsorption study

The method used for in vitro adsorption study was the one described by Toyoguchi et al. (2005) .Adsorbents (30 mg as the component drug) were added to the drug solutions (100 ml) in to the beaker stirring with a magnetic stirrer with the speed of 100 rpm at room temperature. Sampling was done at definite time intervals of 0, 60, 120, 180, 240, 300, 360 and 420 min and suspensions were filtered through a membrane filter (0.45 µ). The concentrations and percentage of drug adsorbed at different intervals on to the adsorbents were measured by spectrophotometric analysis at the maximum absorption wavelength at 319 nm using UV spectrophotometer.

Microbial load test

The adsorbent(s) was taken in test tube with 2 ml of distilled water, vortexed for 5 min and centrifuged at 5000 rpm in Remi centrifugator (Jindal Scientific Industries, Ambala, India) to obtain the supernatant fluid. One milliliter of supernatant fluid was transferred aseptically to the sterilized agar media and incubated at 37^0C for 24 h.A positive control using *Staphylococcus aureus* ATCC (Goat Research Institute, Agra, India) as the bacterial culture and negative control were also maintained.

Preparation of Adsorbates

Adsorbates of secnidazole were prepared using accurel-MP1000, aerosil-200 and microcrystalline cellulose the ratio of 1:1, using physical mixing and solvent deposition methods.

Physical mixing

The adsorbent(s) sifted through mesh no. 120 was mixed with the drug in 1: 1 ratio by weight and physically blended in polybag for time interval 30 min to get adsorbates F1, F2 and F3 prepared using accurel MP 1000, aerosil and MCC respectively that were stored in desiccator until use.

Solvent deposition

Drug dissolved in a minimum volume (2 ml) of solvent was mixed with adsorbent to get a homogeneous mix. The solvent was allowed to evaporate in the rotary flask evaporator (Hicon Enterprises, India) at 40 rpm for 1h at 50^0 C to obtain F4, F5 and F6 adsorbates prepared using accurel MP 1000, aerosil and MCC respectively. The dry masses were kept in a desiccator at room temperature.

Characterization of adsorbates

In vitro drug release

The in vitro release study was accomplished using USP type II method (2000). The dissolution mediums were 900 ml of phosphate buffer pH 4.0, 6.8 and 7.4

Table 3. *In vitro* drug release data of pure drug and adsorbates prepared by physical mixing (F1-F3) in phosphate buffer of varying pH.

Time	pH 4.0				pH 6.8				pH 7.4			
(min)	F0	F1	F2	F3	F0	F1	F2	F3	F0	F1	F2	F3
0	-	-	-	-	-	-	-	-	-	-	-	-
30	90.44 ±0.29	77.54 ±1.3	83.75 ±1.76	79.52 ±0.35	91.04 ±0.64	74.17 ±0.30	81.04 ±0.26	76.71 ±1.00	83.69 ±1.55	69.54 ±1.12	79.48 ±1.17	74.19 ±1.60
60	95.23 ±0.49	86.02 ±0.86	85.19 ±0.36	84.55 ±0.21	92.60 ±0.13	83.55 ±0.22	82.60 ±0.34	84.10 ±0.32	88.92 ±0.26	78.67 ±0.46	81.43 ±0.23	82.27 ±0.16
120	98.92 ±0.78	91.60 ±0.82	91.21 ±0.30	89.99 ±0.1.2	91.98 ±0.81	83.85 ±0.24	88.98 ±1.7	86.43 ±0.22	92.34 ±0.22	81.24 ±0.57	86.59 ±0.54	84.44 ±1.83
180	98.07 ±0.99	89.53 ±0.36	89.42 ±0.49	89.61 ±0.31	91.35 ±1.67	83.86 ±0.89	89.35 ±0.15	89.89 ±1.79	91.56 ±1.9	80.78 ±1.23	87.92 ±0.27	87.38 ±0.21
240	97.86 ±0.23	89.69 ±0.68	94.39 ±0.82	90.96 ±0.90	96.65 ±0.89	84.61 ±2.36	92.29 ±0.80	90.08 ±0.17	94.77 ±0.20	82.68 ±0.84	88.40 ±1.24	87.97 ±0.32
360	97.28 ±1.38	90.65 ±0.77	94.07 ±0.33	89.59 ±0.76	96.29 ±0.79	84.49 ±1.91	91.79 ±0.56	89.22 ±0.44	92.68 ±0.40	82.11 ±2.51	88.94 ±0.45	86.49 ±0.42
480	98.86 ±0.81	89.43 ±0.41	93.88 ±0.54	87.77 ±0.94	96.60 ±0.47	83.93 ±0.21	90.60 ±0.52	89.27 ±0.87	93.76 ±0.74	81.96 ±0.51	87.99 ±0.34	86.43 ±0.21

maintained at 37 ± 0.5^0 C temperature and 75 rpm stirring rate. A weighed amount of the sample (equivalent to 50 mg secnidazole) was dispersed onto the surface of the dissolution medium. At appropriate intervals, 5 ml samples were withdrawn filtered and the concentration of secnidazole was determined spectrophotometrically at 319 nm for phosphate buffers pH 4.0, 6.8 and 7.4 respectively. The average of three experiments was calculated.

Modification of capsule shell and in vitro drug release

Formaldehyde solution (4 % v/v) was poured into the desiccator and allowed to equilibrate for 2 hr. The capsule shells (# 2) placed on stainless steel mesh were exposed to formaldehyde vapors for 2 hr and air dried. Ethanolic solutions of coating polymer, PVP K-40 (2.5, 5.0 and 7.5 % w/v) were prepared for coating of adsorbate-filled formaldehyde stressed capsule through dip coating method. The dip coated capsules were air dried between successive coatings filed with selected adsorbates equivalent to 50mg of SDZ and in vitro release studies were carried out at 37 ± 0.5 ^{0}C for 8 hr using USP type I dissolution rate test apparatus.

Differential scanning calorimetry

The differential scanning calorimetry (DSC) profiles of SDZ, the adsorbents and adsorbates were recorded on Pyris Diamond DSC-4 (PerkinElmer, Wellesley, MA). Thermal behaviors were studied under normal conditions with perforated and sealed quartz pans and with a nitrogen gas flow of 400 ml/min. The samples were heated at 10^{o}C/min over a temperature range of 20^{o}C to 300^{o}C. The reference sample used in all determinations was alumina with a weight of 10.5 mg. Peak temperatures and enthalpies were calculated by calculating the mean of three measurements.

Scanning electron microscopy

SEM photographs were obtained using a JEOL JSM 6100 SM instrument. The samples were sputtered with gold for 15-20 minutes and the photomicrographs were taken under suitable magnification.

Fourier transform infra-red analysis

FTIR spectra of the samples were determined by the KBr pellet method using a Jasco FT761 spectrophotometer (Jasco, Japan) in the range of 400 – 4000cm^{-1}.

Powder X-ray diffraction

The powder diffraction patterns of the samples were obtained using a XPERT Pro instrument, Netherlands. The system was operated at 2 theta scale with a range of 10 - 50^0 C. The powder samples were kept in glass holder cavity.

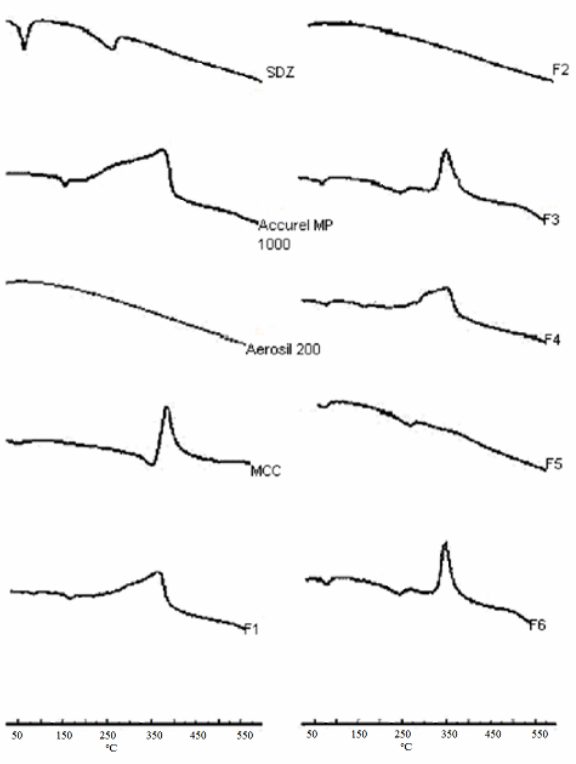

Figure 4. DSC thermograms of (a) SDZ, (b) accurel MP 1000,(c) aerosil2000 (d)MCC ; physically mixed adsorbates(e) F1, (f) F2 (g)F3; and solvent deposited adsorbates (h) F4, (i) F5, and (j)F6

RESULTS AND DISCUSSION

Solubility Study

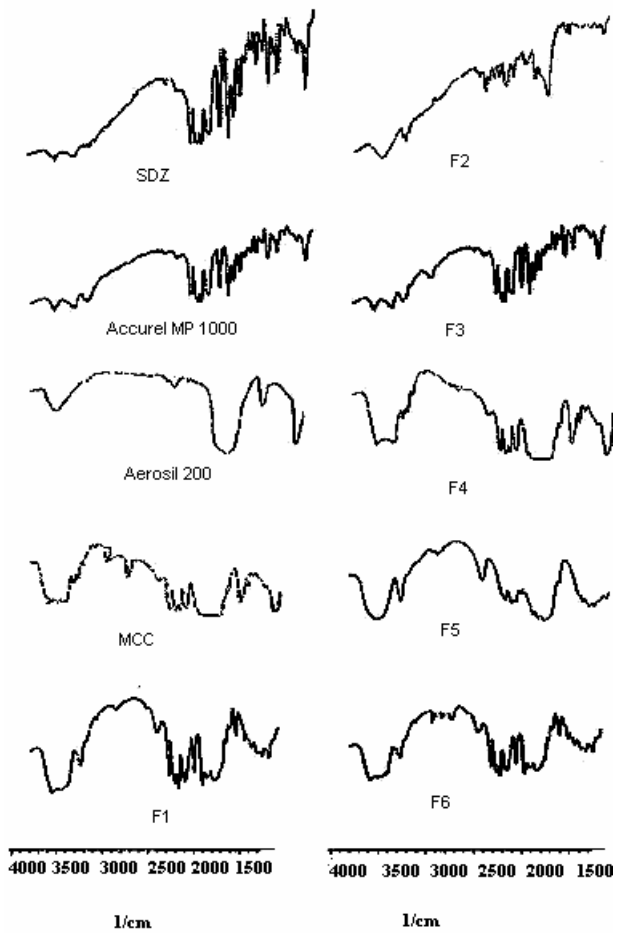

Figure 6. FTIR spectra of (a) SDZ, (b) accurel MP 1000,(c) aerosil2000 (d) MCC ; physically mixed adsorbates (e) F1, (f) F2 (g) F3; and solvent deposited adsorbates (h) F4, (i) F5, and (j) F6

The solubility of drug, when evaluated at variable pH (Table1) clearly indicated a decrease in solubility on increasing pH values that increased insignificantly with time to reach equilibrium values within 72 hours. The increase in solubility may be attributed to decrease in the concentration of the ionized species of the weakly basic drug at high pH and an increase of the unionized form. Further higher solubility of the drug at low pH values can be explained by the presence of polar groups (-OH and $-NO_2$) in the chemical structure of drug, that can form hydrochloride salt in the acidic medium (Wells, 1987). Correspondingly the solubility of drug was found to be 49.88 mg/ml in pH 4.0 phosphate buffer followed by a solubility of 47.72 mg/ml (pH 6.8), 41.06 mg/ml (pH 7.4) and 38.68mg/ml at 9.0 suggesting that the absorption of drug in vivo shall be dissolution rate limited resulting in fluctuations in the plasma concentrations. Thus a system that is able to modulate the solubility of the drug during gastrointestinal passage is desirable.

Screening of adsorbates

In an attempt to screen the adsorbents various tests were performed. The microbial load test of the adsorbents revealed considerable colony forming units (cfu) in the adsorbents obtained from natural sources namely bentonite, silica gel G and kaolin (Table 2). MCC a semisynthetic cellulose derivative showed 4 cfu at the end of 48hr and no cfu were observed for accurel MP 1000 and aerosil 200. Hence the screening of adsorbents was focused on the latter three adsorbents. Particle size measurements revealed z-average diameter which is the mean diameter based on the intensity of scattered light, as 347.2, 830.2 and 3701 nm and polydispersity index (PDI) as 1.000, 0.666 and 1.000 respectively for accurel-MP1000 (microporous polypropylene), aerosil-200 and microcrystalline cellulose (MCC). On the basis of z average accurel MP 1000 was most suited as least value of average diameter was indicative of higher surface area available for modulation of drug release especially a high dose drug. Further the highest value of tapped density was indicative of highly porous structure of the bulk powder that was confirmed by porosity analysis that revealed maximum porosity for accurel-MP1000 (86.15%) followed by aerosil-200 (81.65 %). Highly porous structure of adsorbent supports the concept of pronounced drug loading capacity for making the matrices of controlled release formulations (Armas et al 2000). Evaluation of the flow property of adsorbents by Hausner's index revealed accurel MP 1000 to have the least value of 0.549. Hausner's index is a measure of interparticle friction and lower the values more free flowing is the powder (Aulton 2002) and hence amenable to processing conditions. A measure of adsorptive capacities of the adsorbents further accomplished the superiority of accurel MP 1000 over other adsorbents as it displayed highest adsorptive capacity of 88.62% that it was closely followed by aerosil 200 and MCC (Table 2). The amount adsorbed on accurel MP100 was highest suggesting that the adsorption has taken place onto the outer surface and inside the accurel channel pores. Actually the pore size is large enough to allow access to the large internal surface area of the microporous materials and that the diffusion of SDZ molecules is not restricted by the pore structure. However the relative contribution of each of these two surfaces to the adsorption process was not estimated because adsorption onto the external surface and into the inner pores occurs spontaneously and uniformly as has been reported previously (Renzo et al 1997; Hata et al 1999).

Preliminary studies for preparation of adsorbates

For the preparation of adsorbates physical mixing and solvent deposition methods were utilized. The physical mixing method was optimized for percent drug adsorbed with respect to increasing mixing time until constant levels were achieved for each of the sifted fraction of accurel (BSS mesh no. 85, 100, 120 and 200 of pore diameter 180, 150, 125 and 75 µm respectively). It was observed that the percent free drug decreased as the mixing time increased in steps of 10 min until a constant value was obtained at 30 min that was maintained till the end of 60 min (Figure 1). Hence a mixing time of 30 min was selected for preparation of adsorbates by physical mixing. Similarly for the selection of solvent to be used for solvent deposition method, the drug binding capacity of hydrophilic solvents namely ethanol, methanol, dimethylformamide and dichloromethane was evaluated using accurel MP 1000 as prototype. The drug binding capacity was found to be highest for methanol (0.362g of SDZ/g of AC) subsequently followed by ethanol

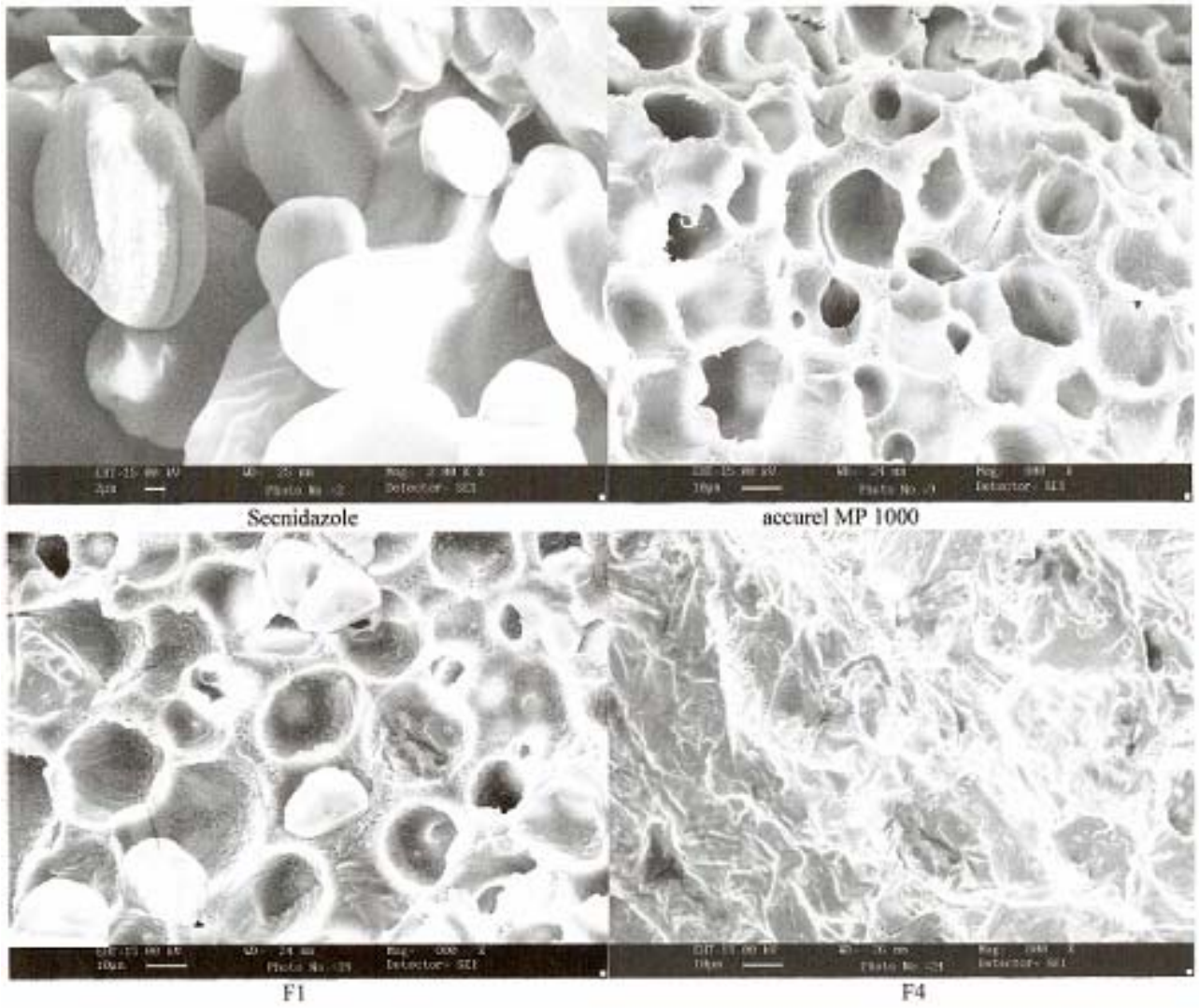

Figure 5. Scanning electron micrographs of SDZ, accurel MP 1000, physically mixed adsorbate, F1 and solvent deposited adsorbate F4.

(0.208g/g), dimethylformamide (0.192g/g) and dichloromethane (0.284g/g). The results are suggestive of the effect of solvent properties on adsorption that have also been reported by Ohta et al. (2005) and Charnay et al. (2004) wherein the workers have reported that the adsorption varies as a function of the solvent properties and thus in the present study it was possible that the interaction between silica and drug was more enhanced in methanol than in rest of the solvents. Thus methanol with maximum binding capacity was the solvent of choice for preparation of solvent deposited adsorbates.

Characterization of Adsorbates

In-vitro dissolution study

In vitro drug dissolution was studied for 8 hrs by powder dispersion technique in pH 4.0, 6.8 and 7.4 phosphate buffers IP. The drug dissolution was highest in pH 4.0 (Table 3, 4) irrespective of the method of preparation of adsorbates that was quite predictable based on solubility results. The dissolution of SDZ was higher than all the adsorbates and the adsorbates prepared by solvent deposition method (F4-F6) exhibited better control on the dissolution at all pH values and the effect was pronounced at pH 7.4 which is the major site of absorption of majority of the drugs. Thus at the end of 480 min the dissolution of SDZ ranged from 68.92%-79.49 % from solvent deposited adsorbates in contrast to 81.96% -87.99% from physically mixed (F1-F3) adsorbates at pH 7.4. This clearly is indicative of the modulation of drug dissolution by use of adsorbents and that has been reported by various workers (Sunada et al 2006; Chauhan et al 2005; Gohel et al 2002). The dissolution of pure drug were extremely high with 98.86% of drug released during 8 hours of the dissolution run in pH 4.0, 96.60% in pH 6.8 and 93.76% in pH 7.4 phosphate buffers respectively**.**

On comparing the dissolution of SDZ from adsorbates at 7.4 the adsorbate F4 made using accurelMP1000 displayed best control on dissolution with only 68.92% being dissoluted at the end of 8 hr followed by the F6 (MCC-SDZ adsorbate) and F5 (Aerosil-SDZ adsorbate). Interestingly adsorbates prepared with Aerosil-200 (F2 and F5) at all pH values displayed highest dissolution.

Aerosil 200 is characterized by surface silanol groups that are capable to forming hydrogen bonds with drug molecules during preparation of adsorbates thereby improving wettability of the drug particles and hence faster drug dissolution (Armas et al 2000). However, the

dissolution from all the adsorbates was non linear when analyzed by PCP Disso 2.0v software, Pune ,India and it best fitted the Peppas model. Thus preparation of adsorbates was not sufficient to achieve controlled delivery of SDZ and to ensure that the drug is released beyond gastric pH and a drug delivery system that was able to delay the release and also deliver the drug in controlled manner was desirable. Thus a delayed release capsule formulations using F4 – F6 were designed for the above said purpose.

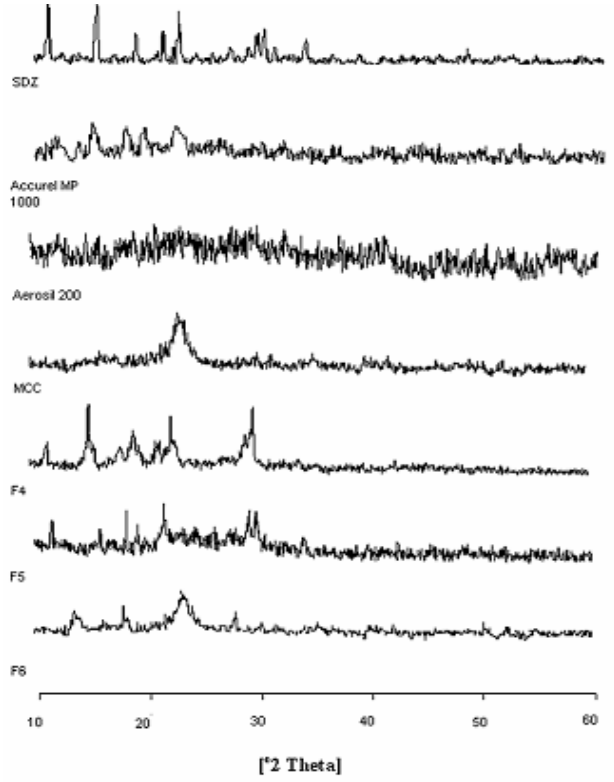

Figure 7. X Ray Diffractograms of (a) SDZ, (b) accurel MP 1000,(c) aerosil 200 (d) MCC ; physically mixed adsorbates(e) F1, (f) F2 (g) F3; and solvent deposited adsorbates (h) F4, (i) F5, and (j) F6

Modification of in-vitro drug release

Gelatin capsule shells (#2) were stressed by exposure to formaldehyde vapours in a dessicator for 2 hr. Formaldehyde is known to react with gelatin and the reaction between formaldehyde and gelatin is followed by an increase in molecular weight and viscosity and a decrease in water absorption capacity, where cross-linking seems to interfere with the natural alignment of molecules. This results in decrease in solubility and resistance in the intestinal tract for gelatin capsules modified with formaldehyde (Pina et al 1996). These stressed capsules can be readily be subjected to coating with a polymeric film by dip coating method that is otherwise not possible for non-stressed capsule and stressed capsules have been reported to modify the drug release as well (Digenes et al 2006).Hence PVP coating was aimed to delay the release and formaldehyde stressed capsule were used for potential modification of drug release pattern.

Thus formaldehyde stressed capsules filled with solvent deposited adsorbates were dip coated with varying strength (2.5, 5, 7.5 % w/v) of coating polymer PVP-K 40 that exhibits pH dependent solubility. It was observed that capsules coated with 2.5 %w/v coating polymer were able to delay the release (beyond 120 min) but the it was non zero order. However, the capsules coated with 5%w/v PVP K-40 displayed a delayed zero order release that was also observed with 7.5% coating strength wherein the delayed effect was more pronounced (Figure 2), but as the aim of delayed release to the duodenal segment could be achieved at lower coating concentrations hence 5%w/v coating strength was selected as the optimized coating concentration for pH-dependent controlled release duodenal delivery of SDZ. When compared to the marketed formulation the optimized formulation showed a better control over the drug release (Figure 3) Though both the formulations displayed a delayed release the optimized formulation was able to maintain zero order release with a maximum release of 95.91% at the end of 8 hr in contrast to marketed formulation that gave a burst release of 67.89% within 2.5 hours followed by a non zero order release of 87.89% at the end of fifth hour. Thus F4 encapsulated in PVP coated formaldehyde treated capsule was identified as superior formulation of secnidazole that has the potential to provide controlled duodenal delivery.

Differential Scanning Calorimetry (DSC)

Thermograms of secnidazole, adsorbents and drug loaded adsorbates were investigated for the molecular state of adsorbed drug (Figure 4). The DSC profile of pure secnidazole revealed two sharp endothermic peaks with an onset melting temperatures of 80^0C and 270^0C. Endothermic peaks corresponding to pure secnidazole could not be clearly identified in F4 but were faintly visible in F1. In F4 prepared by solvent deposition the drug was adsorbed at molecular level in contrast to F1 where the SDZ though adsorbed on acurrel MP was partially in particulate state also. Both F1 and F4 retained the exothermic peak of accurel. Aerosol SDZ adsorbates F2 and F5 and MCC adsorbates F3 and F6 showed reduced intensity endothermic peaks with a slight shift in the onset melting point of SDZ towards lower temperature. This phenomenon is indicative of existence of some interaction between secnidazole and the adsorbent particles in their adsorbates that was further clarified by other spectral studies.

Scanning Electron Microscopy

Surface topography (Figure 5) of SDZ revealed smooth surfaced almost spherical discrete particles whereas surface topography of accurel revealed highly porous structure with pores of almost similar size arranged as a network. The porous network of micro- as well as macropores was almost completely covered with the drug deposited probably at either molecular level or as precipitates in F4 prepared by solvent deposition method. As the solvent evaporated the drug could have precipitated within the pores/channels of the adsorbents in contrast to o physically mixed adsorbate, F1.These micrographs explain the existence of faint endothermic peaks of SDZ in thermogram of F2 that were not distinguishable in F4

FT-IR Spectroscopy

Table 4. *In vitro* drug release data of pure drug and adsorbates (F4-F6) in phosphate buffer of varying pH.

Time (min)	pH 4.0				pH 6.8				pH 7.4			
	F0	F1	F2	F3	F0	F1	F2	F3	F0	F1	F2	F3
0	-	-	-	-	-	-	-	-	-	-	-	-
30	90.44 ±0.29	53.21 ±0.71	79.75 ±0.59	55.92 ±1.37	91.04 ±0.64	47.95 ±0.37	78.84 ±1.16	66.67 ±0.15	83.69 ±1.55	40.16 ±0.40	79.11 ±0.16	77.90 ±1.78
60	95.23 ±0.49	58.37 ±1.08	82.33 ±0.23	60.61 ±0.50	92.60 ±0.13	56.68 ±1.30	79.04 ±0.32	69.16 ±0.29	88.92 ±0.26	53.81 ±3.03	82.33 ±1.35	79.64 ±0.39
120	98.92 ±0.78	72.00 ±0.83	86.22 ±0.77	69.86 ±1.86	91.98 ±0.81	72.00 ±0.18	83.72 ±1.11	73.44 ±0.43	92.34 ±0.22	64.49 ±0.46	80.73 ±1.40	79.70 ±1.14
180	98.07 ±0.99	84.91 ±1.30	95.97 ±0.61	78.54 ±0.33	91.35 ±1.67	75.40 ±1.04	85.16 ±0.26	76.02 ±1.55	91.56 ±1.9	67.83 ±1.74	85.26 ±0.27	75.78 ±2.16
240	97.86 ±0.23	86.75 ±1.07	95.23 ±0.27	85.19 ±0.46	96.65 ±0.89	80.39 ±0.39	88.52 ±1.44	75.22 ±0.23	94.77 ±0.20	70.73 ±0.31	84.18 ±0.20	79.34 ±0.66
360	97.28 ±1.38	89.22 ±0.73	95.59 ±0.38	84.73 ±0.98	96.29 ±0.79	79.09 ±0.19	90.08 ±0.95	75.09 ±1.35	92.68 ±0.40	69.39 ±0.30	84.01 ±0.11	80.83 ±0.27
480	98.86 ±0.81	87.07 ±0.79	94.13 ±1.56	83.44 ±0.50	96.60 ±0.47	82.28 ±1.24	73.44 ±0.81	73.44 ±0.81	93.7 ±0.74	68.92 ±0.40	83.76 ±0.66	79.49 ±0.54

Infra red studies were performed to determine interactions in drug and adsorbents. The IR spectrum of pure Secnidazole (Figure 6) showed the characteristic peaks to -OH group (3512.13 cm^{-1}), -NO_2 group (1531.37 and 1365.51 cm^{-1} for the asymmetric and the symmetric bends, respectively), -CH_3 group (1463.87 cm^{-1} for asymmetric bend), -CH_2 group (1489.0 cm^{-1} for scissors bend) and C-N groups (1267.14 cm^{-1}) (Armas et al, 2000). Characteristic peaks of drug were retained in the IR spectra of adsorbates with some broadening and reduction in intensity as compared to the adsorbates is indicative of physical interaction. However Secnidazole loaded Aerosil-200 adsorbate F5 showed disappearance of peak corresponding to -CN group that may be attributed to some chemical reaction between the silanol group of aerosol and –C-N of SDZ.

X-Ray Diffractrometry

Powder X-ray diffraction patterns (Figure 7) showed numerous distinctive peaks of SDZ. The crystallographic pattern of adsorbates retained the peaks corresponding to SDZ but a decrease in intensity of some major SDZ crystalline peaks (11.35, 15.6, 19, 21.4, 22.8, 30.2 and 33.9^{0}C) was documented. In general the diffractograms of adsorbates F3-F6 were a summation of crystallographic peaks of SDZ and the adsorbate(s) with partial loss of crystallinity of SDZ due to its deposition on adsorbates accompanied by residues of solvents from the precipitation process that can become molecular additions to the crystal and changed its habit.

CONCLUSION

SDZ Accurel MP 1000 adsorbates were prepared by solvent deposition method and formulated as delayed controlled release system by encapsulating in hardened capsule coated with polymeric coating of PVP K-40. The designed system provided delayed release of gastric acid unstable drug and the release started beyond pH 4.0 in a controlled manner. These results suggest that the developed microporous adsorbent system has the potential for targeted release of drugs.

ACKNOWLEDGEMENTS The authors are thankful to Indian Institute of Technology, Rorkee, for providing the instrumental facilities for scanning electron microscopy and X-ray diffraction and DSC.

REFERENCES

1. Adachi, T. and E. Isobe, E. 2004. Fundamental characteristics of synthetic adsorbents intended for industrial chromatographic separations. J. Chromatogr. 1036:33-44.
2. Alsaidan, S.A., Alsughayer, A.A., and G.A. Eshra. 1998. Improved dissolution rate of Indomethacin by adsorbents., Drug Dev Ind Pharm. 24: 389- 394.
3. Rivera, A.B., Hernandez, R.G., Armas, H.N., Elizastegi, D.M.C. and M.V. Losada. 2000.
4. Physicochemical and solid-state characterization of secnidazole. IL Farmaco.
5. 55:700 -707.
6. Aulton, M.E. 2002. Pharmaceutics-The Science of Dosage Form design. Churchill Livingstone, New York.
7. Brar, F.S.K. 2000. Essentials of Pharmacotherapeutics, S. Chand & Company Ltd. New Delhi.
8. Benita, S. 1996. Microencapsulation, Drugs and Pharmaceutical Sciences, Marcel Dekker, New York.
9. Chang, J. and W. Xia. 2006). Well-ordered mesoporous bioactive glasses (MBG): A promising bioactive drug delivery system. J Control Rel. 110: 522-530.
10. Charnay, C., Begu, S., Peteilh, C.T., Nicole, L., Lerner, D.A., Devoisselle, J.M. (2004). Inclusion of ibuprofen in mesoporous templated silica: Drug loading and release property. Eur J Pharm Biopharm. 57, 533-540
11. Chauhan, B., Shimpi, S., and A. Paradkar. 2005. Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with

silicon dioxide by spray drying technique. Eur J Pharm Sci. 26: 219-230.
12. Davis, K.A. and K.S. Anseth. 2002. Controlled release from crosslinked degradable networks. Crit Rev Ther Drug Carr Syst. 19: 385-423.
13. Digenis G. A., Gold, T. B. and V.P. Shah. 2006. Cross-linking of gelatin capsules and its relevance to their in vitro-in vivo performance. J Pharm Sci. 83: 915-921.
14. Friedrich, H., Fussneger, B., Kolter, K., and R. Bodmeier. 2006. Dissolution rate improvement of poorly water-soluble drugs obtained by adsorbing solutions of drugs in hydrophilic solvents onto high surface area carriers. Eur J Pharm Biopharm. 62:171- 177.
15. Gohel, M.C. and L.D. Patel. 2002. Improvement of nimesulide dissolution from solid dispersions containing croscarmellose sodium and aerosil-200. Acta Pharmaceutica. 52:227- 241.
16. Hata, H., Saeki, T., Kimuro, T. Sugahara, Y. and K. Kuroda. 1999. Chem. Mat. 11: 1110-1119.
17. Ito, Y., Kusawake, T., Ishida, M., Tawa, R., Shibata, N. and K.Takada. 2005. Oral solid Gentamicin preparation using emulsifier and adsorbent. J Control Rel. 105: 23 -31.
18. Li, A.M., Zhang, Q.X. and J.L. Chen. 2001. Adsorption of phenolic compounds on Amberlite XAD-4 and its acetylated derivative MX-4, Reactions and Functions of Polymers. 49: 225-233.
19. Martin A. 1999. Physical Pharmacy, B.I. Waverly Pvt. Ltd., New Delhi, India.
20. Masque, N., Galia, M. and R.M. Marce. 1999. Influence of chemical modification of polymeric resin on retention of polar compounds in solid-phase extraction, Chromotographia. 50: 21-26.
21. Ohta, K.M., Fuji, M., Takei, T, and M. Chikazawa. 2005. Development of a simple method for preparation of a silica gel based controlled delivery system with high drug content. Eur J Pharm Sci. 26: 87-96.
22. Pina, M., Souza, A.T. and A.P. Brojo. 1996. Enteric coating of hard gelatin capsules Part2-bioavailability of formaldehyde treated capsules. Int J Pharm. 148:73-84.
23. Renzo Di, F., Cambon,H. and R. Dutartre, R. 1997). A 28 year old synthesis of micelle-templated mesoporous silica. Micropor Mat. 10: 283-286.
24. Salis, A., Sanjust, E., Solinus, V. and M. Monduzzi. 2003. Characterization of Accurel MP 1004 polypropylene powder and its use as a support for lipase immobilization. J Mol Catal B, Enz. 24-25: 75-82.
25. Sharma, S., Sher, P., Badve, S. and A. P. Pawar. 2005. Adsorption of Meloxicam on porous Calcium silicate: characterization and tablet formulation., AAPS Pharm
26. Sci. Tech. 6, 4: E 618 – 625, Article 76.
27. Shen, S., Chow, P. S., Chen, F. and R.B.H. Tan. 2007. Submicron Particles of SBA-15 modified with MgO as carriers for controlled drug delivery. Chem Pharm Bull. 7: 985-991.
28. Sher, P., Ingavle, G., Ponrathnam, S. and A.P. Pawar. 2007. Low density porous carriers Drug adsorption and release study by response surface methodology using different solvents. Int J Pharm.331:72 -83.
29. Streubel, A., Siepmann, J. and R. Bodmeier. 2002. Floating microparticles based on low density foam powder. Int J Pharm. 241: 279-292.
30. Streubel, A., Siepmann, J. and R. Bodmeier. 2003. Floating matrix tablet based on low density foam powder: effect of formulation and processing parameters on drug release. Eur J Pharm. Sci. 18:37-45.
31. Sunada, H., Wang, L. and F.D. Cui. 2006. Preparation and evaluation of solid dispersions of Nitrendipine prepared with fine silica particles using the melt-mixing method. Chem Pharm Bull. 54: 37-43.
32. Toyoguchi, T., Ebihara, M., Ojima, F., Hosoya, J.and Y. Nakagama. 2005. In vitro study of the adsorption characteristics of drugs. Biol. Pharm. Bull. 28: 841- 844.
33. United States Pharmacopoeia 24/National Formulary. 2000. 19th Asian Edition, USP Convention, Rockville (MD).
34. Wells, J.I. 1987. Pharmaceutical Preformulation: the physicochemical properties of drug substances, Wiley, New York.
35. Williams, A.C., Timmins, P., Lu, M. and R.T. Forbes. 2005. Disorder and Dissolution enhancement: Deposition of Ibuprofen onto insoluble polymers. Eur J Pharm Sci. 26: 288 -294.
36. Yuasa, H., Takashima, Y., Kanaya, Y. (1996). Studies on the development of intragastric floating and sustained release preparation. I. Application of calcium silicate as a floating carrier. Chem Pharm Bull. 44, 1361-1366.
37. Zhang, X., Wyss, U.P., Pichora, D. and M.F.A. Goosen. 1994. A mechanism study of antibiotic release from biodegradable poly(D,L-lactide) cylinders. J Control Rel. 31: 129-144.
38. Zheng, K., Pan, B., Zhang Q., Zhang, W., Pan, B., Han, Y, Zhang, Q., Wei, D., Xu, Z. and Q. Zhang. 2007. Enhanced adsorption of *p*-nitroaniline from water by a carboxylated polymeric adsorbent. Sep Purific Tech. 57: 250-256.