AAPS PharmSciTech, Vol. 14, No. 3, September 2013 (© 2013)
DOI: 10.1208/s12249-013-9985-6

Research Article

Porous Starch: a Novel Carrier for Solubility Enhancement of Carbamazepine

Meer Tarique Ali,[1,2] Ritesh Fule,[1] Ajay Sav,[1] and Purnima Amin[1]

Received 20 February 2013; accepted 15 May 2013; published online 29 May 2013

Abstract. To circumvent the solubility-related issues associated with Biopharmaceutics Classification System class II drugs, a novel porous carrier has been developed. In the present study, a process for preparation of porous starch (PS) is demonstrated. The process briefly comprises of translucent gel preparation followed by solvent replacement, drying, and sizing. Carbamazepine (CBZ) was used as a drug candidate to exhibit solubility enhancement potential of PS. PS and CBZ-loaded PS (CBZ-PS) systems were characterized with respect to IR, DSC, XRD, SEM, and dissolution kinetic studies. PS-CBZ was found to follow a Fickian behavior during dissolution. *In vivo* studies conducted in mice displayed a superior performance of CBZ-PS as compared to neat CBZ.

KEY WORDS: carbamazepine; dissolution; solubility enhancement.

INTRODUCTION

Majority of the fraction of newer drug candidate falls into Biopharmaceutics Classification System (BCS) class II drugs which remain a threatening factor to these drugs for reaching market in spite of possessing an excellent therapeutic activity. To solve this issue, literature is growing with burgeoning number of strategies ranging from prodrugs (1), solid solution (2), cyclodextrin complexation (3), mesoporous silica encapsulation (4), pH modulation (5), amorphization (6) to particle size reduction (7). However, each strategy endures from its own demerit such as higher costing, higher ratios of carrier material and stability, *etc.*

Carbamazepine (CBZ) is a first-line drug indicated for epilepsy and trigeminal neuralgia (8). CBZ is listed in the Essential Medicines WHO Model List, Core List, 12th edition (revised April 2002) and is classified as a class II drug according to the BCS (9). CBZ (Fig. 1) is practically insoluble in water (<200 μg/mL). Absorption of CBZ is slow, erratic, and unpredictable in humans, when administered orally, as CBZ shows slow dissolution (10). Many attempts were done in order to improve the bioavailability of CBZ which include but not limited to liquisolid tablet technique (11), SBA-15 pellets (12), nanocrystallization (13), and hot melt extrusion (14).

Starch is one of the most commonly used excipients. Depending on the concentration and method of addition, its use varies such as disintegrant, thickener, binder, and diluent.

Starch carries a combination of amylose and branched amylopectin. Both polymers are arranged in a semicrystalline pattern. The different configuration of amylose and amylopectin results in different behavior in cold aqueous conditions. Amylose exhibits higher tendencies towards crystallization resulting in insoluble adducts, while amylopectin exhibits slow jellification, forming highly translucent and opaque systems over the period.

Starch is a GRAS-, IIG-, and U.S. Pharmacopeial Convention (USP)-listed material and officially acceptable by all major regulatory agencies for its use in various oral drug delivery systems (15).

Prior art reveals various methods of preparation of porous starch (PS), such as enzymatic hydrolysis of noncrystalline regions of granular starch at subgelatinization temperature (16), hot melt co-extrusion of corn starch and starch acetate (17), microwave treatment of starch (18), and supercritical fluid extrusion where supercritical carbon dioxide was used as a blowing agent (19).

Intermolecular bonds of starch can be broken in the presence of heat and water. These broken sites are available to form hydrogen bonds with water. Thus, this water penetration results into decreased crystalline regions within starch and increased randomness which is exhibited by pore formation. Since direct drying of hydrogel may result into collapse of porous structures, water replacement from hydrogel with ethanol to form alcogel is important to maintain the porous structure. Therefore, we have implied a solvent exchange method for the formulation of porous starch.

Since the starch material is economical and readily available, we thought to use it as a carrier for solubility enhancement by incorporating a porous structure within the material. Thus, the present study deals with the preparation of porous starch and its use for the solubility enhancement of CBZ.

MATERIALS AND METHODS

Materials

Carbamazepine (USP) was purchased from Amoli Organics Pvt. Ltd. (India). Sodium lauryl sulfate (USP) and acetone were

[1] Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Matunga (E), Mumbai 400019, India.
[2] To whom correspondence should be addressed. (e-mail: tarique.meer@gmail.com)

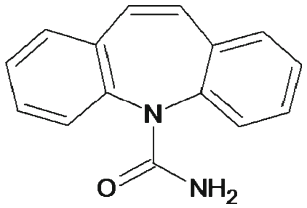

Fig. 1. Structure of CBZ

purchased from S.D. Fine chemicals (India). Starch and sodium starch glycolate were kind gifts from Roquette (France). Polyvinylpyrrolidone (Kollidon 90) was procured from BASF (Germany). Colloidal silicon dioxide and microcrystalline cellulose (Avicel PH-102) were donated by Degussa (Germany) and FMC BioPolymer (Ireland), respectively.

Preparation of PS

PS was prepared as reported earlier with little modification (20). Ten grams of starch was well dispersed in 40 mL of distilled water at room temperature. Sixty milliliters of distilled water was heated to its boiling point. Starch dispersion was then added to the boiling water under rapid stirring. The temperature was steadily brought down to room temperature and the stirring was continued till a translucent gel was formed. The gel was stored in excess water at 8°C overnight so as to attain an equilibrium state. The gel was then subjected for solvent exchange by ethanol. The gel was equilibrated and stored in ethanol at 8°C for 48 h to maintain its porous structure. After achieving the equilibrium state, the gel was then dried using rotary vaporization under a vacuum at 30°C. The dried material was milled and stored in the vacuum till further use. This material is further referred to as PS.

Evaluation of Flow Properties

The flow of neat and porous starch was characterized by angle of repose (θ). A funnel was fixed 5 cm above a base plate. Fifteen grams of powder was placed in a funnel and allowed to pass through it and fall on the base plate so as to form a pile. The height (h) and diameter (d) of the pile were measured, and the angle of repose was determined as follows:

$$\text{Angle of repose } (\theta) = \tan^{-1}\left(2h/d\right). \quad (1)$$

The compressibility index of powder was determined using following equation:

$$\text{Compressibility index } \%(C_i) = (V_i - V_f) \times 100/V_i \quad (2)$$

where V_i is the untapped apparent volume and V_f is the final tapped volume of the sample after tapping the material until no further volume changes were observed.

Specific Surface Area and Pore Size Distribution

The surface area of developed porous starch was determined using nitrogen sorption isotherms through Brumauer–Emmett–Teller (BET) protocol. Nitrogen sorption studies were done using ASAP2020 (Micromeritics, USA). Before initiation of the study, the powder sample was stored in sample bulb and then subjected to 40°C under vacuum of 0.1 mPa overnight to facilitate removal of moisture from the sample. The nitrogen sorption data were generated through a relative pressure ($p/p0$) range of 0.0 to 1.0. The pore size distribution and pore volume were calculated following Barrett–Joiner–Halenda protocol.

Table I. Composition of CBZ-PS Tablet

Ingredients	Quantity mg/tablet
CBZ-PS	200
Microcrystalline cellulose (MCC 102)	78
Polyvinylpyrrolidone (Kollidon 90)	15
Sodium starch glycolate (Glycolys)	15
Colloidal silicon dioxide (Aerosil 200)	3

Drug Loading on PS

Five hundred milligrams of CBZ was dissolved in 10 mL of acetone followed by the addition of 500 mg of PS particles under stirring at 27±2°C. The stirring was continued till acetone evaporates completely leaving behind free-flowing CBZ-loaded PS particles (CBZ-PS).

Formulation of CBZ-PS Tablets

CBZ-PS tablets having composition as shown in Table I were formulated. The tablets were made using a single punch tablet compression machine (Cadmach Machinery, India) with 8-mm standard concave punches. The compression force during formulation of tablets was 10 kN. The crushing strength of tablets was maintained at 5–7 kg/cm^2.

Dissolution Kinetic Studies

The dissolution studies were performed in 900 mL of 1% SLS solution using USP type II apparatus operated at 75 rpm and at 37°C. Sink condition was maintained throughout the study. Each dissolution study was carried out in double triplicate. The aliquots taken at various time intervals were diluted suitably to quantify the drug release spectrophotometrically at 287 nm. The analytical method for CBZ has linearity within the range of 0–20 μg/mL and expressed by the Eq. 3 as follows:

$$A = 0.0502C + 0.0042 \quad (3)$$

where A is the absorbance of the test solution measured at λ_{max} of 287 nm, and C is CBZ concentration in micrograms per milliliter in the test solution.

Table II. Flow Properties of Neat and Porous Starch

Sample	Angle of repose (deg)	Compressibility index (%)
Neat starch	38.69	33.07
PS	18.95	17.93

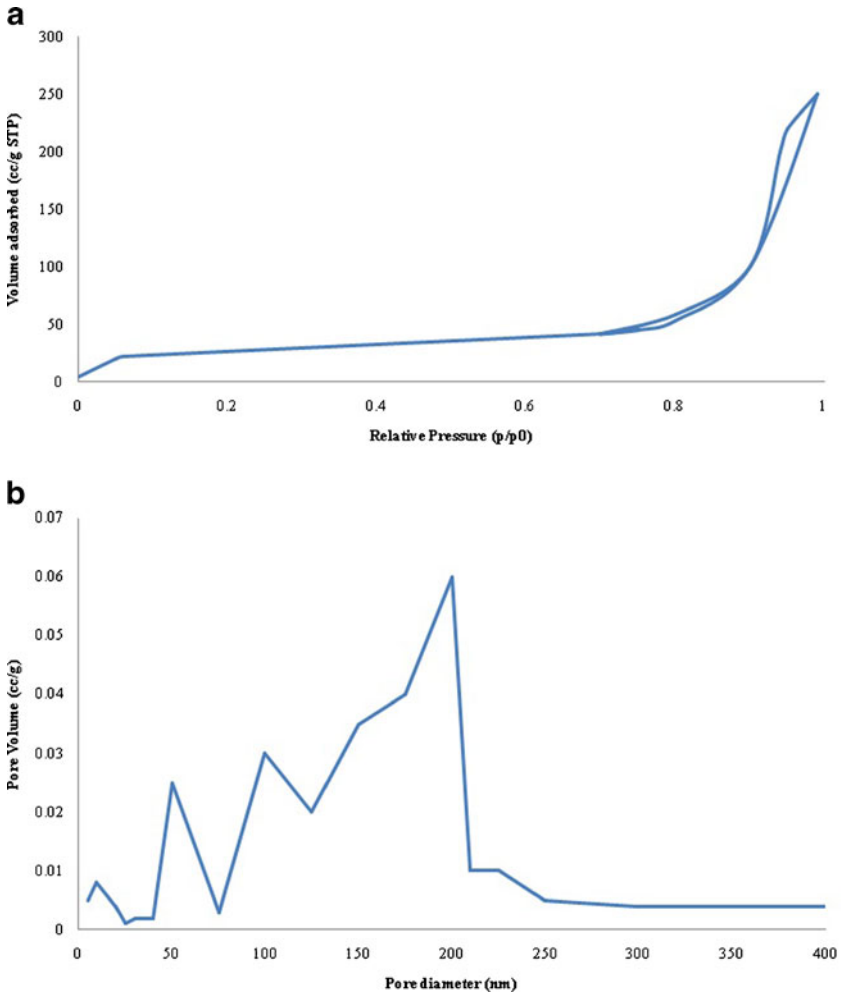

Fig. 2. **a** Nitrogen adsorption isotherm for PS. **b** Pore size distribution of PS

Thermal Studies

Differential scanning calorimeter (DSC) (Pyris 6DSC, PerkinElmer, USA) with a thermal analyzer, equipped with the Pyris software, was employed to obtain thermal data. The instrument was calibrated prior to test the samples, using indium. Five milligrams of sample was placed in a DSC aluminum sample pan and then crimped. Heat flow rate of 10°C/min was used to heat the samples from 40°C to 220°C. Nitrogen was used as a purge gas. An empty crimped pan was used as a reference pan.

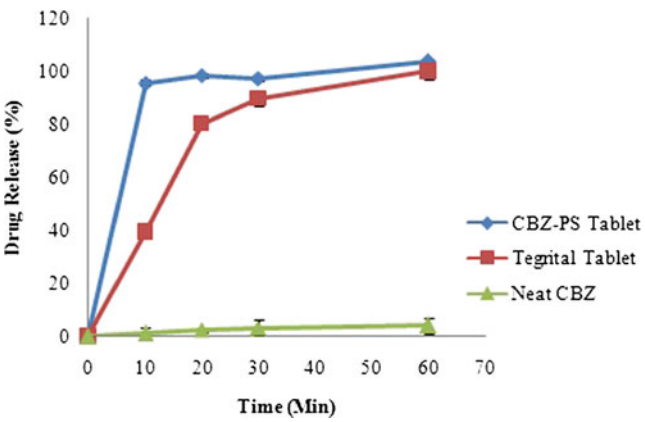

Fig. 3. Dissolution profile of CBZ from various formulations

Scanning Electron Microscopic Studies

Morphology of the particulate samples was evaluated using a scanning electron microscope (SEM; 97 JSM-6380LA, Jeol Ltd., Japan). Double-sided adhesive carbon tape was used to fix the sample powders to an aluminum stub and it was made conductive for use in Jeol Sputter for 5 min at 10 mA by coating with gold and palladium layers in vacuum. The samples were then loaded into the

Table III. Formulation Characterization Using the Korsmeyer–Peppas Equation

System	*k*	*n*
Neat CBZ tablet	0.002	0.702
CBZ-PS tablet	0.865	0.042
Tegretol tablet	0.157	0.475

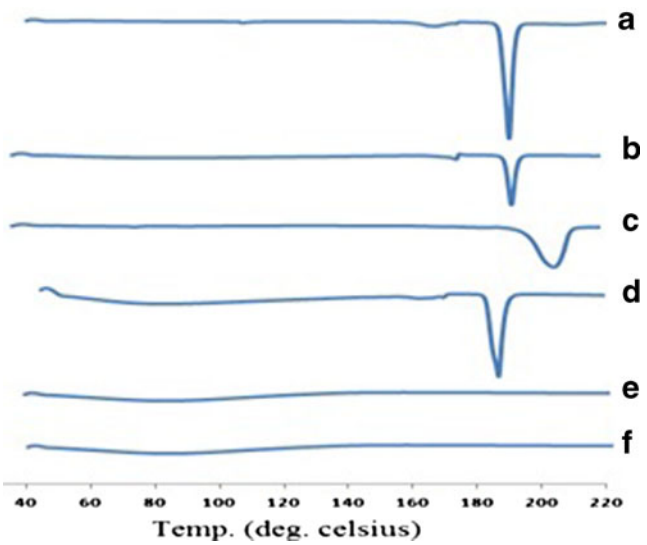

Fig. 4. DSC thermogram of *a* CBZ, *b* CBZ-PS, *c* physical mixture of CBZ and PS, *d* Tegretol, *e* neat starch, and *f* PS

SEM to obtain scanning electron micrographs above ×100 resolution.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectroscopy (FTIR) spectrometer from PerkinElmer (USA) was used in an attenuated total reflectance manner to obtain FTIR spectra. The samples were ground thoroughly with potassium bromide at 1:100 (sample/potassium bromide) weight ratio in a mortar and pestle till a uniform mixture is observed. Scans were performed in triplicate from 4,000 to 400 cm^{-1} at a resolution of 4 cm^{-1}.

Powder X-ray Diffraction Studies

The X-ray diffraction patterns of particulate samples were recorded in a Rigaku powder X-ray diffraction system (Miniflex, Japan) with Cu Kα as a source for radiation. The samples were run over the most in formative range from 5° to 50° of 2θ values. The step scan mode was performed with a step size of 0.02° at a rate of 2°/min.

Determination of Anticonvulsant Activity

The anticonvulsant activity of CBZ, CBZ-PS, and Tegretol was determined using the maximal electroshock method. The use of animals for the study was approved by the animal ethics committee of the Institute of Chemical Technology, Mumbai. The study was conducted in male albino mice having a weight of 25–30 g. Each group was composed of six animals which were fasted overnight prior to the study. CBZ and its formulations were administered orally in a dose of 35 mg equivalent CBZ/kg body weight (11) in the following manner:

Group 1 Half milliliter vehicle (0.25% sodium carboxy methyl cellulose in distilled water) as control
Group 2 Tegretol tablets powdered and then suspended in 0.5 mL vehicle, such that these volumes contained the required dose
Group 3 Neat CBZ in a required dose suspended in 0.5 mL vehicle
Group 4 Received an amount of the powdered CBZ-PS containing the animal dose suspended in 0.2 mL vehicle

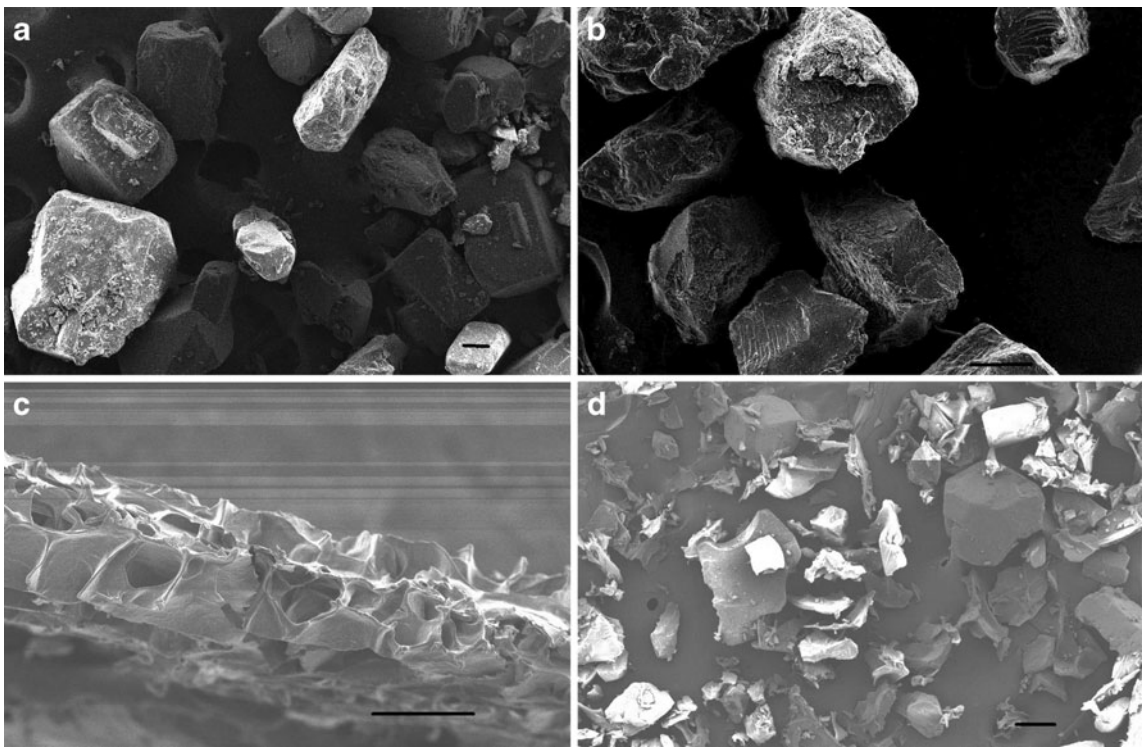

Fig. 5. SEM of **a** neat CBZ, **b** neat starch, **c** PS, and **d** CBZ-PS (*scale bars*=1 μm)

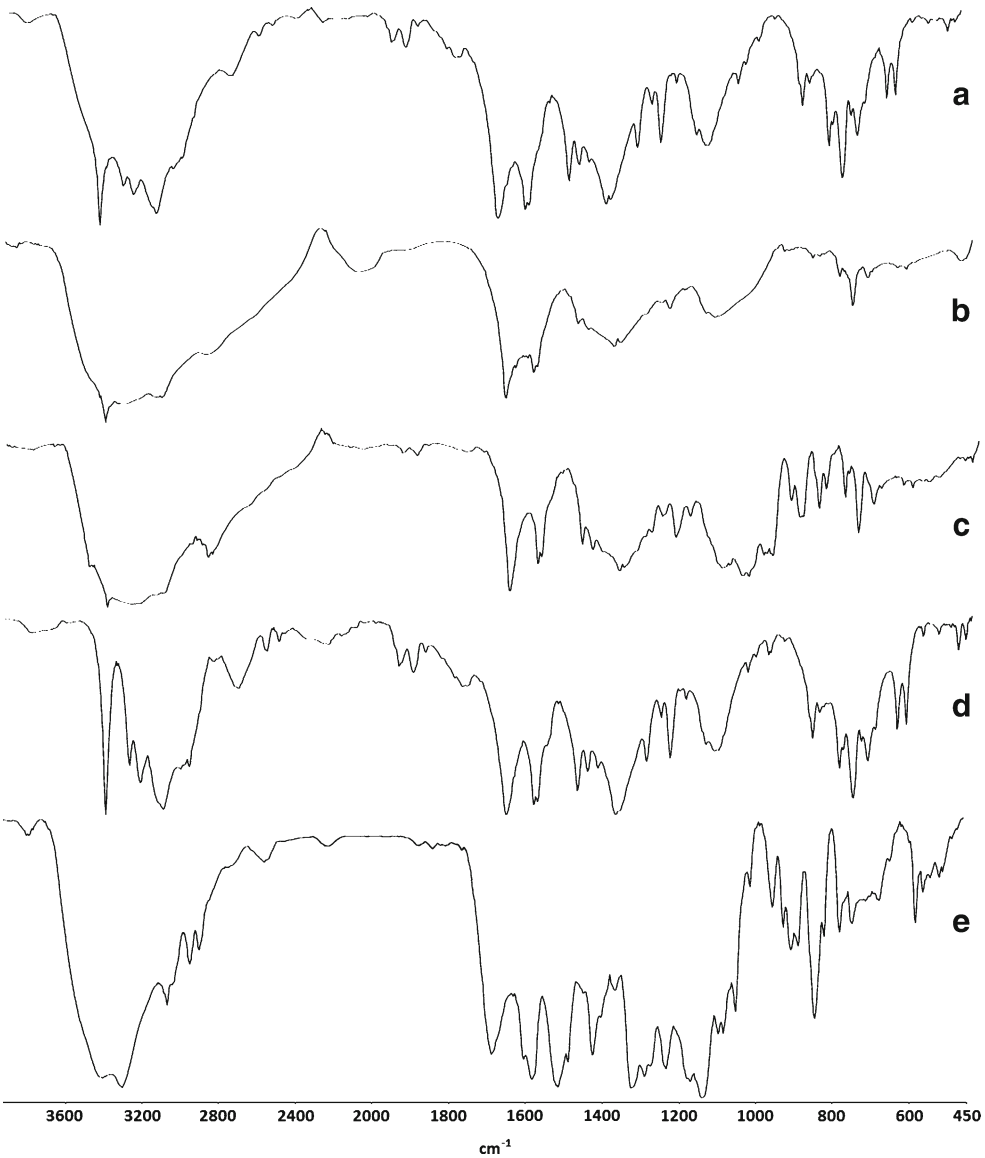

Fig. 6. FTIR of *a* neat starch, *b* PS, *c* CBZ-PS, *d* neat CBZ, and *e* physical mixture of PS and CBZ

Drug or formulation was administered to the animal, and after 1 h, an electrical stimulus (50 mA) was applied for 0.2 s. An electrical simulator was used to deliver maximal electroshock seizure (MES) stimuli. The electrodes were placed at the ear of the animal.

The animals were held firm by hand and freed at the time of stimulation so as to observe for the seizure. The drug could prevent the MES spread if the animal fails to show hind limb tonic extensor.

The results were expressed as percent animals protected.

RESULTS AND DISCUSSION

Evaluation of Flow Properties

Angle of repose and compressibility index are often used as simple, fast, and popular means to predict the flow properties of powders. The smaller values of the angle of repose (≤30°) indicate excellent flow property, whereas low Ci (≤20) signifies fair flow and little cohesiveness (21). Thus, Table II indicates a significant improvement of flow properties of PS as compared to neat starch.

Specific Surface Area and Pore Size Distribution

The nitrogen sorption curve (Fig. 2a) showed type IV isotherm displaying a monolayer adsorption followed by multilayer adsorption of nitrogen on PS. Nitrogen condensation step resulted in two hysteresis loops. The first loop ran from $p/p0$ value of 0.7 to 0.9 and responsible for nitrogen condensation in mesopores (20). The second hysteresis loop ($p/p0$ of 0.9 to 0.99) was relatively hefty, signifying nitrogen condensation within the macropores. Specific surface area determined by the BET method was found to be 109.73 m^2/g. Major populations of the pores were found to be around 200 nm (Fig. 2b) and total pore volume was calculated as 0.32 mL/g.

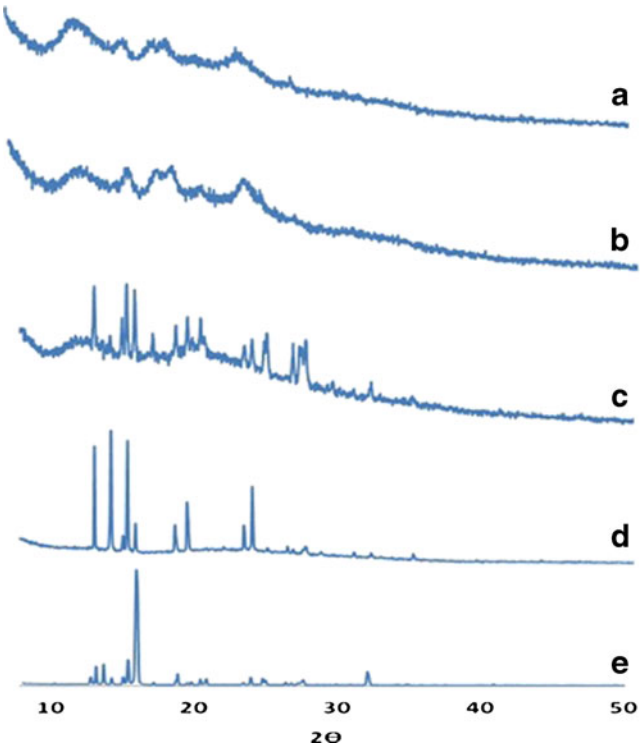

Fig. 7. PXRD of *a* neat starch, *b* PS, *c* CBZ-PS, *d* physical mixture of CBZ and PS, and *e* CBZ

Dissolution Kinetic Studies

Rapid drug release profile was observed in case of CBZ-PS and Tegretol as compared to neat CBZ (Fig. 3). The significantly improved dissolution profile for CBZ-PS might be due to (a) high surface area of drug, (b) geometric confinement of CBZ within the pores of porous starch thereby reducing the CBZ particle size, and (c) decreased crystallinity as evident from the powder X-ray diffraction (PXRD) pattern and improved wettability.

The dissolution data were tried to fit in Korsmeyer–Peppas (Eq. 4) (22) model to identify the release mechanism of CBZ from formulation.

$$M_t / M_\infty = kt^n \tag{4}$$

where M_t/M_∞ is fraction of drug released at time t, k is release constant, and n is release exponent and an indicative of release mechanism.

To declare a system exhibiting Fickian diffusional characteristics, the corresponding value of n should be lower than (23) 0.45 for CBZ-PS indicating the system is following Fick's law of diffusion. Tegretol showed marginally high value of n signifying for slightly non-Fickian release behavior (Table III). Neat CBZ had a significantly high n value illustrating mixed non-Fickian release mechanism.

Table IV. Anticonvulsant Activity Amongst Various Groups

Group number	Number of animals exhibiting convulsion	Protection (%)
1	6/6	0
2	0/6	100
3	4/6	33.33
4	0/6	100

Thermal Studies

Sharp endothermic peak for CBZ was seen from different thermograms. Decreased area under curve corresponding to reduced enthalpy for CBZ in case of CBZ-PS signified that there was little reduction in crystallinity of CBZ. A complexation effect of CBZ in CBZ-PS was mainly responsible for observed modified calorimetric pattern of CBZ-MS. It was evident from the thermal behavior of CBZ (Fig. 4), which took place in three phases. Initially, CBZ (which was in form III) melted at around 174°C then recrystallized to "form I" as shown by an exothermic peak and then again a sharp endothermic peak at 193°C for melting of CBZ form I, concluding that CBZ was in polymorphic monoclinic form III (24). The physical mixture of CBZ and PS resulted in wider and weaker melting peak indicating a dilution effect and little interaction through hydrogen bonding. Both starches, neat as well as porous, showed very subtle thermal behavior and were found to be remained almost unaffected. Tegretol performed in a different way indicating the presence of CBZ in a different form other than "form III."

Scanning Electron Microscopic Studies

Neat CBZ (Fig. 5a) displayed glistening appearance with crystalline coarser particles. The surface of neat starch (Fig. 5b) showed trivial roughness, indicating less likelihood for interaction with other chemical moieties. PS (Fig. 5c) showed spongy morphology which could be positively tendered for interaction with the drug. Figure 5d exhibited a nicely intermingled CBZ within porous starch. Majority of the pore volume and area found to engage with CBZ resulting into suppressed recrystallization of CBZ.

FTIR Spectroscopy

FTIR of the neat starch and PS was found to be comparable as shown in Fig. 6. In case of PS, the intensity of peaks decreased and smoothening of the peaks was observed, when compared with the neat starch. This may be due to the fact that pore formation in PS may have resulted in decreased starch granular density (25). Important peaks (26) characterizing starch are 764 cm^{-1} (C–C stretch), 1,067 cm^{-1} (C–H bending), 1,344 cm^{-1} (C–O–H bending and $-CH_2$ twisting), and 3,165 cm^{-1} ($-CH_2$ deformation) (27). CBZ is characterized by the presence of 3,465 cm^{-1} (–NH2 vibration), 1,677 cm^{-1} (–CO–R vibration), and 1,605 and 1,593 cm^{-1} (–C=C– vibration C=O vibration and deformation of –NH) (9). The presence of peak at 3,161 cm^{-1} signified that CBZ is in its polymorphic form III (24). Hydrogen bonding and steric hindrance are often used as a tool to describe the interaction of drug and carrier (28) and carbonyl group remains a powerful hydrogen bond acceptor (29) which can form a hydrogen bond with the terminal hydroxyl group of glucose units present in porous starch as evident from the decreased peak intensity of carbonyl group and C–H peak broadening in CBZ-PS system.

PXRD Studies

X-ray diffraction (XRD) of CBZ exhibits presence of peaks at 2θ values at with very narrow crystal size as indicated by low peak width. Important 2θ values of CBZ were 13.14, 13.71, 15.03, 15.36, 15.93, 17.17, 18.69, 19.56, 20.56, 22.07, 23.45, 25.00, 26.40, 27.47, 29.44, and 30.08 which revealed the presence of polymorphic form III of CBZ which is in good agreement with literature values (24). The background bump in the XRD pattern corresponding to amorphousness of the compound was found to be gradually increasing from neat CBZ, physical mixture of CBZ, and PS to CBZ-PS system. The amorphous systems contain more free energy which often serves as a driving potential for solubility; therefore, these systems are more soluble as compared to that of their crystalline counterpart (30) (Fig. 7).

In Vivo Anticonvulsant Activity

The MES method used to determine anticonvulsant activity is simple, precise, rapid, and reliable as compared to the other methods reported elsewhere such as the use of pharmacodynamic markers (31), direct cortical stimulation (32), and electroencephalogram (33). The outcome for *in vivo* anticonvulsant activity by MES method is shown in Table IV. The anticonvulsant activity for CBZ-PS was found to be excellent and comparable with that of Tegretol. This might be due to improved solubility and dissolution rate of CBZ from CBZ-PS making CBZ readily available for absorption.

Literature is well entrenched with the porous starch formulation strategies. However, these methods pose problems of multiple freezing cycles (34), longer periods of equilibration (20), crosslinking of starch (35), and equipment intensiveness (19). On the contrary, the present method is facile, less time consuming, cost effective, and industrially feasible.

CONCLUSIONS

A successful process has been developed to prepare PS from neat starch. In the present study, successful use of PS is demonstrated for the solubility improvement of CBZ. The developed CBZ-PS systems were characterized with respect to dissolution kinetics, SEM, XRD, IR, and DSC. CBZ-PS systems showed an improved *in vivo* performance as compared to Tegretol and neat CBZ. Thus, PS can be used as a solubility enhancer and carrier for various other drug candidates.

ACKNOWLEDGMENTS

The authors would like to thank University Grants Commission, Government of India, for their financial support.

REFERENCES

1. Hussain A, Rytting JH. Prodrug approach to enhancement of rate of dissolution of allopurinol. J Pharm Sci. 1974;63(5):798–9.
2. Alonzo DE, Gao Y, Zhou D, Mo H, Zhang GG, Taylor LS. Dissolution and precipitation behavior of amorphous solid dispersions. J Pharm Sci. 2011;100(8):3316–31.
3. Jadhav GS, Vavia PR. Physicochemical in silico and in-vivo evaluation of danazole-β cyclodextrin complex. Int J Pharm. 2008;2008(352):5–16.
4. Ambrogi V, Perioli L, Pagano C, Marmottini F, Ricci M, Sagnella A, *et al.* Use of SBA-15 for furosemide oral delivery enhancement. Eur J Pharm Sci. 2012;46(1–2):43–8.
5. Tatavarti AS, Hoag SW. Microenvironmental pH modulation based release enhancement of a weakly basic drug from hydrophilic matrices. J Pharm Sci. 2006;95(7):1459–68.
6. Murdande SB, Pikal MJ, Shanker RM, Bogner RH. Solubility advantage of amorphous pharmaceuticals: II. Application of quantitative thermodynamic relationships for prediction of solubility enhancement in structurally diverse insoluble pharmaceuticals. Pharm Res. 2010;27(12):2704–14.
7. Meer TS, Sawant KP, Amin PD. Liquid anti solvent precipitation process for solubility modulation of bicalutamide. Acta Pharma. 2011;61(4):435–45.
8. Moffat AC, Osselton MD, Widdop Clarke B. Analysis of drugs and poisons, vol. II. London: Pharmaceutical Press; 2004. p. 747–49.
9. Ambrogi V, Perioli L, Marmottini F, Accorsi O, Pagano C, Ricci M, *et al.* Role of mesoporous silicates on carbamazepine dissolution rate enhancement. Microporous Mesoporous Mater. 2008;113(1–3):445–52.
10. Achumecher GE. Therapeutic drug monitoring. New York: Appleton and Lange; 1995. p. 345–95.
11. Tayel SA, Soliman II, Louis D. Improvement of dissolution properties of carbamazepine through application of liquisolid tablet technique. Eur J Pharm Biopharm. 2008;69(1):342–7.
12. Wang Z, Chen B, Quan G, Li F, Wu Q, Dian L, *et al.* Increasing the oral bioavailability of poorly water-soluble carbamazepine using immediate-release pellets supported on SBA-15 mesoporous silica. Int J Nanomedicine. 2012;7(1):5807–18.
13. Wang M, Rutledge GC, Myerson AS, Trout BL. Production and characterization of carbamazepine nanocrystals by electrospraying for continuous pharmaceutical manufacturing. J Pharm Sci. 2012;101(3):1178–88.
14. Xu L, Ming L, Zhefei G, Lin H, Xin F, Chuanbin W. Improving the chemical stability of amorphous solid dispersion with cocrystal technique by hot melt extrusion. Pharm Res. 2012;29(3):806–17.
15. Rowe RC, Shesky PJ, Quinn ME. Handbook of pharmaceutical excipients. 6th ed. London: Pharmaceutical Press; 2009. p. 685–90.
16. Uthumporn U, Zaidul ISM, Karim AA. Hydrolysis of granular starch at sub-gelatinization temperature using a mixture of amylolytic enzymes. Food Bioprod Process. 2010;88(1):47–54.
17. Guan JJ, Hanna MA. Extruding foams from corn starch acetate and native corn starch. Biomacromolecules. 2004;5(6):2329–39.
18. Torres FG, Boccaccini AR, Troncoso OP. Microwave processing of starch based porous structures for tissue engineering scaffolds. J Appl Polym Sci. 2007;103(2):1332–9.
19. Manoi K, Rizvi SSH. Physicochemical characteristics of phosphorylated cross-linked starch produced by reactive supercritical fluid extrusion. Carbohydr Polym. 2010;81(3):687–94.
20. Wu C, Wang Z, Zhi Z, Jiang T, Zhang J, Wang S. Development of biodegradable porous starch foam for improving oral delivery of poorly water soluble drugs. Int J Pharm. 2011;403(1–2):162–9.
21. The United States Pharmacopeia (USP29). 29th ed. Rockville, MD: United States Pharmacopeial Convention Inc.; 2006.
22. Ahuja N, Katare OP, Singh B. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. Eur J Pharm Biopharm. 2007;65(1):26–38.
23. Korsemeyer RW, Gurney R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(1):25–35.
24. Grzesiak AL, Lang M, Kim K, Matzger AJ. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. J Pharm Sci. 2003;92(11):2260–71.
25. Zhang B, Cui D, Liu M, Gong H, Huang Y, Han F. Corn porous starch: preparation, characterization and adsorption property. Int J Biol Macromol. 2012;50(1):250–6.
26. Vasko PD, Blackwell J, KoenigInfrared JL. Raman spectroscopy of carbohydrates: part II: normal coordinate analysis of α-D-glucose. Carbohydr Res. 1972;23(3):407–16.

27. Cael SJ, Koenig JL, Blackwell J. Infrared and Raman spectroscopy of carbohydrates: part III: Raman spectra of the polymorphic forms of amylose. Carbohydr Res. 1973;29(1):123–34.
28. Dinunzio JC, Miller DA, Yang W, Mcginity GW, Williams RO. Amorphous compositions using concentration enhancing polymers for improved bioavailability of itraconazole. Mol Pharm. 2008;5(6):968–80.
29. Chan L, Caixia L, Yuan L, Jian-Feng C. Formation of bicalutamide nanodispersion for dissolution rate enhancement. Int J Pharm. 2011;404(1–2):257–63.
30. Corrigan OI, Holohan EM. Amorphous spray-dried hydroflumethiazide-polyvinylpyrrolidone systems: physicochemical properties. J Pharm Pharmacol. 1984;36(4):217–21.
31. Clinckers R, Smolders I, Meurs A, Ebinger G, Michotte Y. Quantitative in vivo microdialysis study on the influence of multidrug transporters on the blood–brain barrier passage of oxcarbazepine: concomitant use of hippocampal monoamines as pharmacodynamic markers for the anticonvulsant activity. J Pharmacol Exp Ther. 2005;314(2):725–31.
32. Hoogerkamp A, Vis PW, Danhof M, Voskuyl RA. Characterization of the pharmacodynamics of several antiepileptic drugs in a direct cortical stimulation model of anticonvulsant effect in the rat. J Pharmacol Exp Ther. 1994;269(2):521–8.
33. Paschoa OED, Mandema JW, Voskuyl RA, Danhof M. Pharmacokinetic-pharmacodynamic modeling of the anticonvulsant and electroencephalogram effects of phenytoin in rats. J Pharmacol Exp Ther. 1998;284(2):460–6.
34. Qian D, Chang PR, Ma X. Preparation of controllable porous starch with different starch concentrations by the single or dual freezing process. Carbohydr Polym. 2011;86(3):1181–6.
35. Qian D, Anderson DP, Ma X. Preparation and properties of the succinic ester of porous starch. Carbohydr Polym. 2012;88(2):604–8.