Preparation and Evaluation of Orodispersible Tablets Containing Hydroxylbutyl-β-Cyclodextrin-Simvastatin Solid Dispersion

Khaled M Hosny¹,3*, Ahmed Khames²,3 and Seham S Abd Elhady¹
¹Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, King Abdulaziz University, Jeddah, ²Department of Pharmaceutics, Faculty of Pharmacy, Taif University, Taif, Saudi Arabia, ³Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt.

*For correspondence: Email: Elswaify2000@yahoo.com; Tel: +966592722634; Fax: +96626951696

Received: 28 May 2013 Revised accepted: 19 July 2013

Abstract

Purpose: To formulate simvastatin orodispersible tablets with high dissolution rate and enhanced bioavailability.

Methods: Simvastatin solid dispersions in β-cyclodextrin, hydroxypropyl-β-cyclodextrin, and hydroxybutyl-β-cyclodextrin were prepared in different drug: polymer ratios by kneading and solvent evaporation methods. Compatibility was investigated by Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). Based on the results of solubility studies, the most suitable solid dispersion was selected and formulated into orodispersible tablets using Emcosoy and Karpolacin as superdisintegrants, and mannitol and Pullulan as diluents. The tablets were evaluated for wetting and disintegration times, water absorption, and in vitro dissolution.

Results: Increase in drug solubility was dependent on polymer type, concentration and preparation method. Simvastatin-hydroxybutyl-β-cyclodextrin solid dispersion mixture prepared in 1:2 drug: polymer ratio by solvent evaporation method had a higher solubility than other dispersions. DSC and FTIR indicated the formation of solid dispersion without chemical interaction between simvastatin and polymer. Orodispersible tablet prepared with Emcosoy and Pullulan showed least wetting and disintegration times (20 and 35 s, respectively), fastest water sorption rate, and the highest dissolution rate (100 % after 20 min).

Conclusion: Orodispersible tablets prepared with Emcosoy as superdisintegrant and Pullulan as diluents and containing simvastatin solid dispersion in hydroxybutyl-β-cyclodextrin provides optimum water solubility and hence, drug bioavailability.

Keywords: Simvastatin, Emcosoy, Hydroxybutyl-β-cyclodextrins, Pullulan, Polacrillin, Orodispersible, Solid dispersion

INTRODUCTION

Oral route is the simplest and most convenient way of drug administration, with potential manufacturing cost savings [1]. Orally disintegrating systems are dosage forms, which when placed in the mouth, rapidly disperse or dissolve in saliva without the need of water or chewing and can be swallowed in the form of liquid [2]. After disintegration, the drug solution can be partially or completely absorbed from the sublingual mucosal blood vessels and bypasses the first pass metabolism of the liver [3], or be absorbed from the gastrointestinal tract after swallowing [4].
Simvastatin is widely used in the treatment of dyslipidemia as an adjunct to diet. It acts by specific inhibition of 3-hydroxy-3-methyl-glutaryl coenzyme-A (HMG CoA) reductase. It is practically water insoluble crystalline compound (BCS Class II drug) and the dissolution is the rate-limiting step that controls its oral absorption. Therefore, improvement in solubility and dissolution rate is essential to enhance drug bioavailability [5].

Solid dispersion is a technique that depends on melting or dissolution process to disperse one or more active ingredients in a carrier or matrix in the solid state [6]. This ensures increased drug wettability, and the reduction of particle aggregation and hence increased drug dissolution [7]. Cyclodextrins (CDs) are cyclic α-1,4 linked oligosaccharides of α-D-glucopyranose units that have a relatively hydrophobic central cavity and hydrophilic outer surface [8]. CDs are classical examples of compounds that form stable inclusion complexes with a guest molecule [9].

Emcosoy is natural soy polysaccarides, that have no starch or any sugar and contains 75 % dietary fiber. In tablet manufacture; it had evidence of a fast and efficient disintegration power over an extended range of hardness values with improved dissolution characteristics. Polacrillin Potassium is a derivative of crosslinked polymer of polycarboxylic acids. In contact with aqueous media; it shows a very high swelling power leading to a very fast disintegration without the formation of lumps.

In the present investigation simvastatin solid dispersions in cyclodextrins were prepared and optimized by different techniques, the solid dispersions were formulated into orodispersible tablet, using emcosoy and potassium polacrillin as superdisintegrants and evaluated in order to enhance the dissolution rate and bioavailability of simvastatin.

**EXPERIMENTAL**

**Chemicals**

Simvastatin was Kindly supplied by (Saja Pharmaceuticals Co. Ltd., Jeddah, Saudi Arabia). β-cyclodextrins (β-CD), hydroxypropyl-β-cyclodextrins (H-p-β-CD), and hydroxybutyl-β-cyclodextrins (H-b-β-CD) were kindly supplied by (Nihon Shukohin Kako Co., Ltd., Japan). Pullulan (DMV International, Veghel, The Netherlands). Emcosoy (RS PHARMA GmbH & Co. KG Rosenberg Germany). Polacrillin Potassium (Libraw Pharma, New Delhi, India), Mannitol (Merck, Darmstadt, Germany), Saccharine Sodium from Caesar and Loretz (Hilden, Germany) and Aerosil from Degussa (Frankfurt/M., Germany). Other chemicals and reagent were purchased from Sigma-Aldrich (St Louis, MO).

**Preparation of simvastatin solid dispersion**

Solid dispersions of simvastatin in β-CD, H-p-β-CD, and H-b-β-CD were prepared by kneading, and solvent evaporation methods as follows:

**Solvent evaporation method**

Drug and polymer were mixed in the ratios (1:1, 1:2, and 1:3) in a glass mortar methanol was added portion wise with constant continuous stirring until the mixture completely dissolved. Methanol was evaporated under reduced pressure and the resultant solid dispersions were collected [10].

**Kneading method**

In a glass mortar, 50% ethanol solution was added portion wise to the calculated polymer amount according to the selected drug/polymer ratio with triturating until a slurry like consistency was obtained. The drug was incorporated into the slurry and triturating was further continued for 1 h, air dried at 25 °C for 48 h and the resulting dried product was pulverized and passed through 80 mesh sieve [11].

**Solubility studies**

Excess samples of plain simvastatin and the drug-solid dispersions were separately shaken for 48 h in 5 ml water at room temperature. Subsequently, the suspension was centrifuged at 15000 rpm for 30 min and 1 ml filtrate diluted properly with methanol. The diluted solutions were spectrophotometrically analyzed at 238 nm.

**Evaluation of solid dispersion**

Based on the results of solubility studies, the solid dispersion mixture showing superior solubility was selected and subjected to further evaluation by DSC and FTIR, and for drug content and in vitro release.

**Differential scanning calorimetry (DSC)**

DSC thermograms for samples of plain simvastatin, H-b-β-CD, their physical mixture, and solid dispersion were recorded and analyzed. Approximately, 2 mg of samples were weighed into DSC aluminum pans and were
crimped followed by heating under nitrogen flow (20 ml/min) at a heating rate 10°C/min from 40 - 400°C. Aluminum pan containing the same quantity of indium was used as a reference. DSC studies were carried out using DSC instrument (DSC-60, having TA60 software, Shimadzu, Koyto, Japan).

**Infrared spectroscopy (FTIR)**

Drug and various polymers were thoroughly mixed with 300 mg of potassium bromide, compressed to a 2 mm semitransparent disk and placed in the light path for 2 min. The FTIR spectra were recorded over the wave length range from 400 to 4000 cm⁻¹ using FTIR spectrometer (Perkin Elmer Spectrum One, Model 16 PC, Germany).

**Drug content**

A pre-weighed quantity (10 mg) of the prepared solid dispersion was extracted into methanol and filtered (0.22 mm membrane filter disc - Millipore Corporation). The solid dispersion content was determined by measuring absorbance at 238 nm.

**In vitro release studies**

The drug release rate from the solid dispersion was carried out in Erweka-USP dissolution testing apparatus II (paddle method) using 500 ml of phosphate buffer (pH = 6.8) as a dissolution medium at 50 rpm; the temperature was kept constant at 37 ± 0.1 °C. Aliquots (5 ml) were withdrawn at pre-determined time intervals of 5, 10, 15, 30, 45, 60, 70, and 90 mins with replenished on each occasion with the same volume of dissolution fluid [12]. The absorbance of the drug in the samples was measured spectrophotometrically at 238 nm. The mean of six determinations was taken.

**Preparation of simvastatin orodispersible tablets**

Simvastatin orodispersible tablets were prepared using the novel superdisintegrants Emcosoy, and Polacrillin potassium by direct compression. According to the composition shown in Table 1, eight orodispersible formulations of simvastatin were prepared. Preweighed amount of the prepared solid dispersion equivalent to 10 mg simvastatin was mixed with all ingredients in a cubic mixer by geometrical dilution for 10 min. The mixture was directly compressed on a flat 10-mm punch/die set of a tableting machine (Erweka Tablet Press-Type EK0) without granulation.

**Evaluation of simvastatin orodispersible tablets**

**Weight variation**

Twenty tablets were randomly selected from each formulation and separately weighed (Shimadzu digital balance BL-220H) and their average weight and standard deviation were calculated.

**Thickness**

Ten tablets from each formulation were randomly taken and their diameter and thickness were measured at two different positions with a micrometer screw gauge. The average value was then calculated.

**Drug content**

For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to single dosage unit was extracted with methanol and simvastatin.

**Table 1: Composition of simvastatin orodispersible tablets**

| Ingredient                | Formula | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---------------------------|---------|----|----|----|----|----|----|----|----|
| Simvastatin SD            |         | 170| 170| 170| 170| 170| 170| 170| 170|
| Emcosoy                   |         | 0  | 15 | 30 | 45 | 0  | 15 | 30 | 45 |
| Polacrillin Potassium     |         | 45 | 30 | 15 | 0  | 45 | 30 | 15 | 0  |
| Pullulan                  |         | 75 | 75 | 75 | 75 | 0  | 0  | 0  | 0  |
| Mannitol                  |         | 0  | 0  | 0  | 0  | 75 | 75 | 75 | 75 |
| Aerosil                   |         | 3  | 3  | 3  | 3  | 3  | 3  | 3  | 3  |
| Saccharin Sodium          |         | 3  | 3  | 3  | 3  | 3  | 3  | 3  | 3  |
| Magnesium stearate        |         | 3  | 3  | 3  | 3  | 3  | 3  | 3  | 3  |
| Talc                      |         | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| **Total**                 |         | 300| 300| 300| 300| 300| 300| 300| 300|
content was determined as previously mentioned in calculating drug content in the prepared solid dispersion.

**Hardness**

The average breaking strength (kg/cm²) of ten tablets of each formula was determined by hardness tester (ERWEKA, Germany).

**Friability**

Ten tablets from each batch were accurately weighed and placed in the drum of a friabilator (Erweka, Germany) rotated at 25 rpm for a period of 4 min, then dusted, and reweighed. The percentage weight loss was calculated and taken as a measure of friability.

**In vitro dispersion time**

Ten tablets were separately placed in a 25 ml beaker containing 10 ml of distilled water (pH = 6.8) at 37 ± 0.5°C and the time required for complete dispersion was determined.

**Wetting time and water absorption ratio** [13].

Tables were separately weighed (Wₐ) and carefully placed onto the surface of a piece of tissue paper twice folded in a 5 cm diameter petri dish containing 6 ml of aqueous amaranth solution. The time (in seconds) for complete wetting (water reaches the upper surface of the tablet) was noted and recorded as the wetting time. The wetted tablet was carefully removed and reweighed (W₇). Water absorption ratio (R) through the tablet was then determined according to Eq 1.

\[ R = 100 \times \frac{(W₇ - Wₐ)}{Wₐ} \]  

(1)

**In vitro release studies**

The drug release rate from the prepared orodispersible tablets was carried out in Erweka-USP dissolution testing apparatus II (paddle method) following the same conditions applied to determine the drug release rate from the prepared solid dispersion. For comparison T 50%, and T 90% were calculated and compared.

**Statistical analysis**

Statistical analysis was performed using SPSS version 18 software for Windows (SPSS, Inc., Chicago, IL). Differences among group means were analyzed for statistical significance using one-way ANOVA followed by the Tukey-Kramer Multiple Comparisons Test. Differences were considered significant if p < 0.05.

| Table 2: Characteristics of the prepared solid dispersions |
|------------------------------------------------------------|
| Polymer          | D:P | Code | Sₚn (mg) | D.C (%) | Code | SEv (mg) | D.C (%) |
|------------------|-----|------|----------|---------|------|----------|---------|
| β-CD             | 1:1 | F1a  | 2.254    | 97.2    | F1b  | 4.523    | 98.5    |
| β-CD             | 1:2 | F2a  | 4.686    | 96.4    | F2b  | 6.312    | 97.1    |
| β-CD             | 1:3 | F3a  | 5.714    | 97.2    | F3b  | 7.324    | 98.1    |
| H-p-β-CD         | 1:1 | F4a  | 4.333    | 98.1    | F4b  | 6.314    | 98.1    |
| H-p-β-CD         | 1:2 | F5a  | 5.954    | 98.2    | F5b  | 8.943    | 98.2    |
| H-p-β-CD         | 1:3 | F6a  | 6.826    | 97.6    | F6b  | 9.645    | 97.1    |
| H-β-CD           | 1:1 | F7a  | 6.113    | 96.6    | F7b  | 9.876    | 98.2    |
| H-β-CD           | 1:2 | F8a  | 9.223    | 98.2    | F8b  | 12.324   | 97.6    |
| H-b-β-CD         | 1:3 | F9a  | 10.114   | 97.3    | F9b  | 13.107   | 99.4    |

D.C (%) = solubility (µg/ml) for kneading method; SEv = solubility (µg/ml) for solvent evaporation method; *molar drug/polymer ratio; **drug content.
RESULTS

Solubility studies

Effect of solid dispersion, polymer type, preparation method, and drug polymer ratio on the drug water solubility was studied and the results (Table 2) showed that the drug solubility was increased in all prepared solid dispersion mixtures, and the increment of drug solubility was proportional to the polymer concentration.

Based on these results, simvastatin-hydroxybutyl-β-cyclodextrin solid dispersion prepared in 1:2 drug: polymer ratio by solvent evaporation method was selected and subjected to further evaluation by DSC and FTIR, and for drug content, and in vitro release.

Compatibility

Figure 1 shows the DSC thermograms and FTIR spectra of simvastatin, H-b-β-CD, their physical mixture, and the prepared solid dispersion. Simvastatin shows a sharp endothermic melting peak at 138 °C. This peak was retained in the thermogram of the physical mixture with no appearance of new peaks, which means there was no incompatibility. In the solid dispersion thermogram, the peak completely disappeared. FTIR spectrum of simvastatin showed the main characteristic peaks at 3553 cm⁻¹ (free O–H stretching vibrations); 3011, 2959, and 2872 cm⁻¹ (C–H stretching vibrations); and 1714 cm⁻¹.

Drug content

Results of drug content (Table 2) showed excellent loading capacity of the drug into the polymer matrix in the prepared solid dispersion independent of the polymer type and preparation method. The percentage drug content ranged from 96.4% to 99.4. Figure 2 shows the effect of cyclodextrin complexation on the release profiles of simvastatin from the prepared solid dispersion in different ratios. Results indicated that the release rate of simvastatin was significantly increased when dispersed in different cyclodextrin derivatives. Hydroxybutyl derivative of cyclodextrin showed higher solubility than hydroxyl propyl derivative than cyclodextrin and the higher the polymer concentration in the prepared solid dispersion the faster the release rate occurred.

Physicochemical properties of simvastatin orodispersible tablets

The formulated tablets exhibited low weight variation (295 to 311 mg), drug content was between 98.32 – 101.37 % with low standard deviation values; the thickness of tablets varied from 2.2 to 2.4 mm. All formulations showed good mechanical resistance and breaking strength, while friability values were all < 1 % and varied between 0.213 - 0.465 %; hardness was in the range of 3.78 - 2.41 Kg/cm² that lies within acceptable USP limits.

The behavior of the prepared simvastatin orodispersible tablets in contact with water was studied by measuring wetting time, water sorption rate, in vitro dispersion time, and drug release rate from the tablets. Results are summarized in Table 3.

DISCUSSION

Simvastatin solid dispersion with hydroxyl butyl derivative of cyclodextrin showed higher solubility more than solid dispersion prepared with hydroxyl propyl derivative and by cyclodextrin; The solid dispersion made by solvent evaporation method was superior to that prepared by kneading method. Hydroxy-butyl-β-CD has surfactant-like properties owing to the hydrophilicity of its exterior surface which can lower the interfacial tension between poorly soluble drugs and the dissolution medium, resulting in a higher dissolution rate. β-CD with longer C-2 substituted group increased the hydrophilic character of the molecule and hence stronger surfactant action on drug/water contact angle was expected and higher dissolution rates.
Figure 2: (A) Dissolution Profiles of the Pure simvastatin (○), and from solid dispersions F7a (■), F8a (∆), F9a (●), F7b (▲), F8b (●), F9b (●); (B) Dissolution Profiles of the Prepared Orodispersible Tablet Formulations F1 (-), F2 (■), F3 (∆), F4 (○), F5 (x), F6 (●), F7 (∆), F8 (○).

Table 3: Hydrophilic properties of simvastatin orodispersible tablets

| Batch | Wetting time (s) | Water sorption ratio | In vitro dispersion time (s) | Drug release (%) in 5 min | T50% (min.) | T90% (min.) |
|-------|-----------------|----------------------|-----------------------------|---------------------------|-------------|-------------|
| F1    | 40 ±4           | 70±5                 | 68 ±2                       | 30.2 ±3.21                | 11.23       | 27.34       |
| F2    | 35 ±3           | 65±3                 | 50 ±2                       | 25.3 ±2.12                | 13.76       | 24.54       |
| F3    | 24 ±3           | 76±2                 | 41 ±3                       | 54.7 ±3.53                | 4.27        | 11.34       |
| F4    | 20 ±2           | 82±3                 | 35 ±4                       | 60.5 ±2.32                | 3.75        | 9.75        |
| F5    | 56 ±3           | 46±2                 | 77 ±2                       | 31.3 ±4.13                | 11.56       | 29.24       |
| F6    | 50 ±4           | 51±3                 | 75 ±2                       | 33.4 ±4.23                | 10.54       | 20.65       |
| F7    | 42 ±4           | 57±1                 | 64 ±3                       | 38.3 ±2.93                | 8.23        | 18.43       |
| F8    | 37 ±3           | 62±2                 | 56 ±2                       | 48.9 ±4.23                | 5.57        | 13.35       |

obtained. This explained the better solubility results of hydroxy-butylated β-CD than hydroxy propylated form [14].

Despite the fact that formula F9 prepared in 1:3 drug/polymer ratio showed a higher solubility results, it was not selected for further study because the tablet weight in orodispersible formulation is a critical factor and restricted to a certain degree that not affect patient compliance and due to the formula F9 contain polymer in large amount so the amount of solid dispersion require to be incorporated in the tablet will be very large).

In the DSC thermograms of solid dispersion, the peak completely disappeared indicating formation of solid dispersion and conversion of drug from crystalline to amorphous state. The disappearance of the drug melting peak also indicates that it penetrated into H-b-β-CD cavity replacing the water molecule [15].

The main characteristic peaks of simvastatin FTIR spectrum were retained in physical mixtures and SD, which clearly indicate that no chemical interaction occurred between pure drug and polymer in SD

Simvastatin orodispersible tablets were prepared using the novel superdisintegrants Emcosoy, and Polacrillin potassium either alone or in combinations by direct compression.

Emcosoy is natural soy polysaccharides, that have no starch or any sugar and contains 75 % dietary fiber. It is an ideal choice for low calorie and diabetic applications. In tablet manufacture; it had evidence of a fast and efficient disintegration power over an extended range of hardness values with improved dissolution characteristics [16].

Polacrillin Potassium is a derivative of crosslinked polymer of polycarboxylic acids. In contact with aqueous media; it shows a very high swelling power leading to a very fast disintegration without the formation of lumps. It imparts excellent strength to the tablet and has
anti-adherent characteristics that prevent sticking to the dyes and punch [17].

Water insoluble diluents such as microcrystalline cellulose and dicalcium phosphate were excluded from the preparation of orodispersible formulations due to the expected objectionable feeling of grittiness in the mouth. Soluble diluents, mannitol and Pullulan were selected as diluent. Pullulan, a linear glucosic polysaccharide with high water solubility is an edible, bland and tasteless polymer[18].

All the developed simvastatin orodispersible formulations were acceptable and their behavior in contact with water was very good as indicated by the short wetting time, rapid water sorption rate and a short disintegration time.

Wetting time is an indication of the hydrophilicity of the inner structure of the tablet and excipients used. Thus wetting time of a dosage form is related to contact angle. The lower the wetting time the quicker is the tablet disintegration [19]. The disintegration time of orodispersible tablets ranges from 5 – 30 s [20].

The dissolution profiles of different simvastatin orodispersible tablet formulae indicate a higher, faster, and maximum drug release from formula F4 and F3 followed by F8 and F7, where the percentage of drug release reached 100%, 99.1%, 96.2% and 95.8% respectively after 20 min. These results correlate with wetting and disintegration time data, and it reflects the effect of different formulation factors on tablet hydrophilicity.

Further analysis of dissolution data indicate that batches F4, F3, and F8 shows that initial rapid drug release reached 60.5, 54.7, and 48.9 %, respectively after 5 min. This can be attributed to the higher hydrophilic properties and stronger swelling power of Emcosoy in these formulations, while the presence of the very hydrophilic Pullulan as diluent in batches F4 and F3 resulted in a higher initial drug release. The release rate was also dependent on the Pullulan proportion in both formulations. F8 contained mannitol as diluent showed lowest initial drug release due to its lower hydrophilicity than pullulan.

Statistical analysis of T90 was made to test for the significance of the detected difference between the prepared tablet formulations. The results show that the detected difference was significant between all prepared formulations except that between F1, F2, and F5 and also that between F3, F4, and F8 as well as that between F6 and F7. These results indicate that superdisintegrant type is the main factor that affects the release of drug from the prepared tablets rather than its ingredient ratio, and that the effect of diluent type on drug release was insignificant.

CONCLUSION

H-b-β-CD is an efficient polymer to prepare simvastatin solid dispersion and the preparation method together with the drug polymer ratio are critical and significantly affect drug solubility release. The use of suitable superdisintegrants for the preparation of fast-dissolving tablets is critical, as evidenced by the effect of Emcosoy. Similarly, the use of a suitable diluent such as Pullulan promotes water contact which is bery critical for hydrophobic drugs.

REFERENCES

1. Ahmad Zaheer, Maurya Naveen, Mishra K. Santosh, Khan Imran. Solubility enhancement of poorly water soluble drugs: A review. Int J Pharm Tech 2011; 3(1): 807-823.
2. Bandari S, Muttapalli RK, Gannu Rao YM. Orodisperisible tablet: An overview. Asian J Pharm. 2008; 2: 2-11.
3. Gohel M, Patel M, Amin A, Agarwal R, Dave R, Baryna N. Formulation design and optimization of mouth dissolving tablets of nimesulide using vacuum drying technique. AAPS Pharm Sci Tech. 2004; 5(3): 10–15.
4. Berner B, Birudaraj R, Shen S, Li X. Buccal permeation of buprisone: mechanistic studies on transport pathways. J. Pharm. Sci. 2005; 94: 70-78.
5. Prasad Tandale, Dipti Joshi, Gaud RS. Formulation and Evaluation of Extended Release Solid Dispersions Containing Simvastatin. Asian J Biom Pharma Sci 2011; 1(3): 13-19.
6. Ansari MT, Sunderland VB. Solid dispersions of dihydroartemisinin in polyvinylpyrrolidone. Arch. Pharm. Res. 2008; 31(3): 390-398.
7. Rashmi D., Ashish P., Sanjay N.. Formulation and evaluation of mouth dissolving tablets containing amlopidine besylate solid dispersion. Int. J. ChemTech Res. 2010; 2(1): 706-715.
8. Fernandes CM, Teresa VM, Veiga FJ. Physicochemical characterization and in vitro dissolution behavior of nicardipine–cyclodextrins inclusion compounds. Eur J Pharm Sci. 2002; 15: 73–88.
9. Guosong C., Ming J. Cyclodextrin-based inclusion complexation bridging supramolecular chemistry and macromolecular self-assembly. Chem. Soc. Rev. 2011; 40: 2254-2266.
10. Patel RP, Patel MM. Physico-chemical characterization and in vitro dissolution behaviour of Simvastatin β- cyclodextrin inclusion compounds. Drug Deliv Technol. 2007; 7(5): 50-56.
11. Veiga F, Teixeira-Dias JC, Kedzierewicz F, Sousa A, Maincent P. Inclusion complexation of tolbutamide with -cyclodextrin and hydroxypropyl–cyclodextrin. Int. J. Pharm. 1996; 129: 63-71.
12. Patil JS, Kattimani VK, Shiralashetti SS, Marapur SC, Kamarapu MV. Utilization of Superdisintegrants in the Design, Evaluation and Optimization of Orodispersible Tablets containing Simvastatin- Cyclodextrin Inclusion Complexes. Rguhs J Pharm Sci. 2011; 1(3): 209-215.
13. Battue SK, Repay MA, Mauder S, Rio MY. Formulation and evaluation of rapidly disintegrating tablet
Fenoverine tablets: Effect of superdisintegrants. Drug. Dev. Ind. Pharm. 2007; 33: 1225-1232.

14. Bhanja SB, Ellaiah P, Martha SK, Sahu A, Padhy SK. Preparation and Evaluation of Solid Dispersions of Poorly Soluble Drug Repaglinide. Asian J Bioch. Pharm Res 2011; 3(1): 201-221.

15. Yan B., Gui X., Hong, S., Ai H., Hong M. . Effect of Substituted Group of β-Cyclodextrin Derivatives on the Dispersing of Carbon Nanotubes. J Disp Sci Tech 2010; 31(3): 353-358.

16. Raun P, Yang B, Guang MF, Dan Z. Improving the solubility of amelopsin by solid dispersions and inclusion complexes. J Pharma Biomed analy, 2005; 38: 457-464.

17. Hardik P., Viral S. and Umesh U.. New pharmaceutical excipients in solid dosage forms – A review. Int. J. Pharm. Life Sci. 2011; 2(8) :1006-1019.

18. Vineet B., Mayank B., Sharma PK. Formulation and Evaluation of Fast Dissolving Tablets of Amlodipine Besylate Using Different Super Disintegrants and Camphor as Sublimating Agent. Amer-Eur J Scient Res, 2010; 5(4): 264-269.

19. Cheng KC, Demirci A, Catchmark JM. Pullulan: biosynthesis, production, and applications. App MicroBiotech, 2011; 92(1): 29-44.

20. Radke RS, Jadhav JK, Chajeed MR. Formulation and evaluation of orodispersible tablets of baclofen. Int J Chem Tech Res., 2009; 1: 517-521.