International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 10, Issue 5, 2018

Original Article

FORMULATION, OPTIMIZATION, AND EVALUATION OF SITAGLIPTIN AND SIMVASTATIN RAPIDLY DISSOLVING TABLETS

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Received: 26 Jun 2018, Revised and Accepted: 14 Aug 2018

ABSTRACT

Objective: The scope of this work was to formulate sitagliptin and simvastatin rapidly dissolving tablets. However, simvastatin is practically insoluble in water. For improving its poor oral bioavailability and with the aim of facilitating administration to patients facing problems with swallowing rapidly dissolving tablets were prepared

Methods: Tablets were prepared using superdisintegrant addition technique using croscarmellose sodium (Ac-di-sol), sodium starch glycolate (explotab) and crospovidone in different percentages. Evaluation tests such as weight variation, thickness, and content variation, and friability, disintegration, wetting time, *in vitro* dispersion and *in vitro* dissolution were carried out.

Results: The results showed that the presence of crospovidone could enhance the dissolution rate of simvastatin greatly. The best-optimized formulae found were that F8, F9, and F10 which showed good disintegration and the dissolution rate of simvastatin and sitagliptin was more than 90% after 10 min while the dissolution rate for simvastatin and sitagliptin pure standards was 12% and 30%, respectively after 10 min.

Conclusion: Some tablet formulae showed acceptable pharmacotechnical properties and complied with compendium requirements. Results of dissolution studies revealed that F8-F10 showed an increase in the dissolved sitagliptin and simvastatin to be more than 90% after 10 min.

Keywords: Simvastatin, Sitagliptin, Rapidly dissolving tablets, Superdisintegrants, Crospovidone

DOI: http://dx.doi.org/10.22159/ijap.2018v10i5.28122

INTRODUCTION

Many patients with type 2 diabetes are affected by hypercholesterolemia. Therefore, the combination of antidiabetic and anti-hypercholesterolemia is appreciated as Juvisync® convenient tablets which are a combination of sitagliptin and simvastatin. In this work, sitagliptin and simvastatin rapidly dissolving tablets were formulated to achieve faster release than the convenient tablets and more suitable for elderly patients who face difficulty in swallowing. The literature lacks trials of the formulation of simvastatin and sitagliptin combination in rapidly dissolving tablets dosage form.

There are different technologies used for manufacturing fast-dissolving tablets, such as freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition [1, 2]. In this work, simvastatin, and sitagliptin rapidly dissolving tablets were prepared using the easiest technique which is superdisintegrant addition.

Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetra-hydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a] pyrazine phosphate (1:1) monohydrate, with the structural formula shown in fig. 1. Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β (2S*,4S*),-8aβ]], with the structural formula [3] shown in fig. 2.

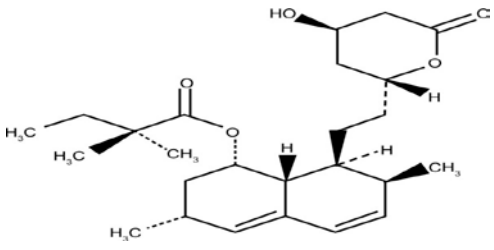

Fig. 1: Chemical structure of simvastatin

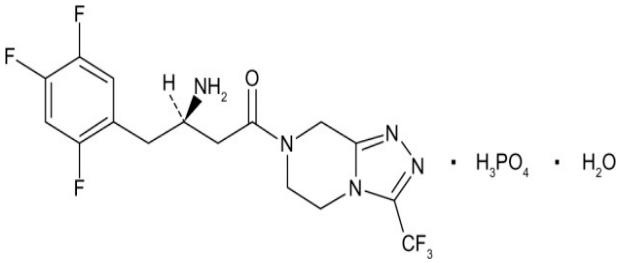

Fig. 2: Chemical structure of sitagliptin phosphate monohydrate

MATERIALS AND METHODS

Materials

Simvastatin and sitagliptin phosphate monohydrate purchased from Virdev, India. Explotab, microcrystalline cellulose (avicel PH 101), croscarmellose sodium (ac-di-sol), lactose monohydrate, magnesium stearate and crospovidone; kindly supplied by; Memphis pharmaceutical chemicals company, Cairo, Egypt. Acetonitrile for HPLC; Merck, Darmstadt, Germany. Hydrochloric acid, phosphoric acid, potassium dihydrogen phosphate; El-Nasr pharmaceutical chemicals company, Cairo, Egypt. High purity water was prepared by using a Waters Milli-Q plus purification system.

Methodology

Development of HPLC assays

Two methods were developed to determine drug content of simvastatin and sitagliptin, dissolution rate in combination.

Preparation of standard solution

40 mg simvastatin and 100 mg sitagliptin were weighed accurately, transferred into a 100 ml measuring flask, 50 ml methanol was added, shaken to dissolve by sonication for 5 min, completed the volume with methanol and mixed well.

Preparation of test solution

Ten tablets were weighed, and the average weight of one tablet was found out and ground. A weight of powdered tablet equivalent to the weight of one tablet was transferred into a 100 ml volumetric flask, about 50 ml methanol was added, sonicated for 15 min, completed the volume using methanol, mixed well and filtered through 0.45 µm membrane filter.

Chromatographic conditions

The separation was achieved using a Kromasil ®, USA C18 (5 µm, 25 cm × 4.6 mm) column, Waters HPLC apparatus consisting of pump 1525 and a UV/VIS detector 2487. The injection volume was 100 µl and a mobile phase consisting of acetonitrile: water 65:35 and adjust pH to 4 with phosphoric acid while at a flow-rate of 0.8 ml/min in case of simvastatin and 1.2 ml/min in case of sitagliptin which was detected at 266 nm while simvastatin was detected at 235 nm. Linearity ranges were 10–70 µg/ml and 5–30 µg/ml for sitagliptin and simvastatin, respectively.

Tablets preparation

Simvastatin and 50% of diluents were mixed and sieved using sieve No. 30 then kneaded with butylated hydroxyanisole dissolved in the least amount of alcohol. Then dried in an air oven till no odor of ethanol, then at a temperature not exceeding 50 ° C and sieved using sieve No. 30. The dried, sieved granules were mixed geometrically with the rest of diluent, disintegrant and sieved using sieve No. 30 and finally mixed with sieved lubricant (magnesium stearate).

Tablets were compressed on flat punch 10 mm. All tablets were compressed into 330-mg using a single punch tablet machine [Erweka, Germany]. The force of compression was kept constant throughout the compression process shown in table 1.

Table 1: Formulae of the rapidly dissolving simvastatin and sitagliptin tablets

Formula	Diluent		Disintegrant		
	Avicel PH 101 (mg)	Mannitol (mg)	Explotab (mg)	Ac-di-sol (mg)	Crospovidone
F 1	123.1	------	30	--------	--------
F 2	123.1	------	------	30	--------
F 3	123.1	------	-------	--------	30
F 4	--------	123.1	30	--------	------
F 5	------	123.1	--------	30	--------
F 6	--------	123.1	--------	------	30
F7	45	48.1	--------	--------	60
F 8	28	35.1	--------	--------	90
F 9	23	30.1	--------	--------	100
F10	13	20.1	--------	--------	120

*each tablet contains 128.5 mg sitagliptin phosphate monohydrate, 40 mg simvastatin, 0.4 mg butylated hydroxyanisole, 2 mg aspartame and 6 mg magnesium stearate

Evaluation of post-compression properties

Weight variation

Twenty tablets, from each formula, were individually weighed [Sartorius, Gottingen, Germany]. The mean weight of the tablets was calculated [4].

Content uniformity

The uniformity of content was determined by crushing ten tablets from each formula and determining the drug content of each tablet individually using the developed HPLC method [4].

Friability

Ten tablets of each formula were accurately weighed and placed in the drum of a friablator [Pharma Test, Germany], which rotated at 25 rpm for a period of 4 min. The tablets were then brushed and reweighed. The percentage loss in weights was calculated and taken as a measure of friability [4].

Hardness

Ten tablets of each formula were tested for their hardness [Tablet Hardness Tester, Erweka, Germany]. The mean hardness in kilograms was then determined [4].

Disintegration time

The disintegration time for each of six tablets of each formula was determined using the USP disintegration tester [USP Disintegration, Pharma Test, Germany] [4].

***In vitro* dispersion time test**

Ten ml measuring cylinder was taken in which 6 ml distilled water was added then a tablet was dropped on it. The time for the tablet to completely disintegrate into fine particles was determined. Three tablets from each formulation were tested, and results were expressed in seconds [5, 6].

Wetting time

Five circular tissue papers of 10 cm diameter were placed in a Petri dish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye were added to Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the uppermost surface of the tablet was determined [6].

Water absorption ratio

A piece of tissue paper was folded twice and placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper. The wetted tablet was then weighed. Water absorption ratio (R), was calculated by the following equation:

$$R = 10(Wa / Wb)$$

Where Wb is the weight of the tablet before water absorption and Wa is the weight of the tablet after water absorption [7].

***In vitro* dissolution studies**

The test was performed in 10 mm sodium phosphate buffer containing 1% tween 80 with 50 µg/ml butylated hydroxyanisole at a temperature of 37°C±0.5°C using the USP dissolution tester [Dissolution Apparatus Validata SR 6, Hanson Research Corporation, USA]. Apparatus II (paddle), at a rotation of 50 rpm [8]. Aliquots, each of 5 ml of the dissolution medium were withdrawn at 5, 10, 15, 20, 30 and 45 min intervals. The samples withdrawn were then filtered, adequately diluted and analyzed for sitagliptin and simvastatin by developed HPLC assays. A similar volume of medium was added to the dissolution medium in order to maintain sink conditions, and a correction factor was included [9].

RESULTS AND DISCUSSION

Formulations post-compression properties were shown in table 2. All formulations were evaluated for weight variation and results indicated very low weight variation which lies within pharmacopeia limits±5%, this may be due that all formula were prepared by wet granulation. Hardness was seen to be in the range of values of 4.3 to 6.4 kg/cm3. Friability of all formulae was less than 1% and the disintegration time of formulae tablets F8-F10 was in the range of 31 to 43 s where crospovidone was in percent of 27-36% of the tablet weight, which may be because crospovidone has been proved to result in fast volume expansion and hydrostatic pressures allowing tablet disintegration [10]. *In vitro* dispersion time of formulae tablets, F8-F10 was in the

range of 40 to 59 sec. wetting time was in the range of 48 to 130 sec. Water absorption ratio was in the range of 40% to 149%.

The dissolution rate of simvastatin Q_{10} from F9, F10 formulae was more than 90% and shown in fig. 3, this may be, because of the increase in the concentration of crospovidone resulted in the particles were exposed to dissolution medium at the comparatively faster rate. Also, the presence of crospovidone in the dissolution medium kept the drug particles in dispersed condition, i.e., aggregation of drug particles was avoided and also increase the wetting of dispersed particles due to fixation of hydrophobic drug particles upon hydrophilic crospovidone during the tabletting process resulting primarily in improvements of dissolution and bioavailability due to enhanced solubility [11].

In comparison with the previous studies of researchers such as Prasanthi S, *et el* [12] prepared simvastatin and sitagliptin tablets by direct compression using pregelatinized starch and explotab as disintegrant, the optimized formula showed dissolution rate of 71.25% and 69.56% for simvastatin and sitagliptin, respectively after 10 min while in my study the dissolution rate was more than 90% after 10 min for both simvastatin and sitagliptin in the formulae F7, F8, and F9. This comparison proved that there is a significant improvement in my work regarding the dissolution rate.

Table 2: Physicochemical properties of the prepared tablets

Formula	Tablet weight*(mg)	Hardness* (kg/cm3)	Disintegr-tion time* (s)	Drug content* (%)	Wetting time* (s±SD)	Water absorption ratio* (%)±SD	*In vitro* dispersion time* (s)	Friability*
F1	329±0.22	5.3±0.05	210±1.19	99.54±0.82	130±0.0	40±0.31	260±0.55	0.125±0.12
F2	330±0.45	5.6±0.26	190±0.95	97.30±1.01	114±0.3	47±0.35	260±0.32	0.012±0.31
F3	331±0.55	5.2±0.34	164±1.13	99.39±1.31	112±1.2	43±1.22	245±0.25	0.097±0.26
F4	332±0.19	4.8±0.09	140±1.34	98.92±1.21	101±1.0	30±1.2	230±0.34	0.175±0.36
F5	330±0.33	5.3±0.08	131±1.19	99.0±1.08	93±0.22	35±0.23	210±0.79	0.071±0.19
F6	329±0.6	5.9±0.12	110±1.25	96.96±1.28	±0.1481	36±0.14	112±0.17	0.157±0.1
F7	331±0.29	4.3±0.15	90±1.13	98.09±1.07	74±0.11	71±0.51	108±0.23	0.089±0.16
F88	329±0.6	5.1±0.11	43±0.93	99.60±1.33	61±0.22	84±0.36	59±0.42	0.39±0.12
F9	330±0.18	6.1±0.21	32±0.22	100.14±0.5	50±0.14	140±0.12	46±0.21	0.084±0.25
F10	332±0.18	6.4±0.11	31±0.12	98.09±1.07	48±0.22	149±0.12	40±0.17	0.175±0.36

*All values are reported as mean±standard deviation (SD), n=5.

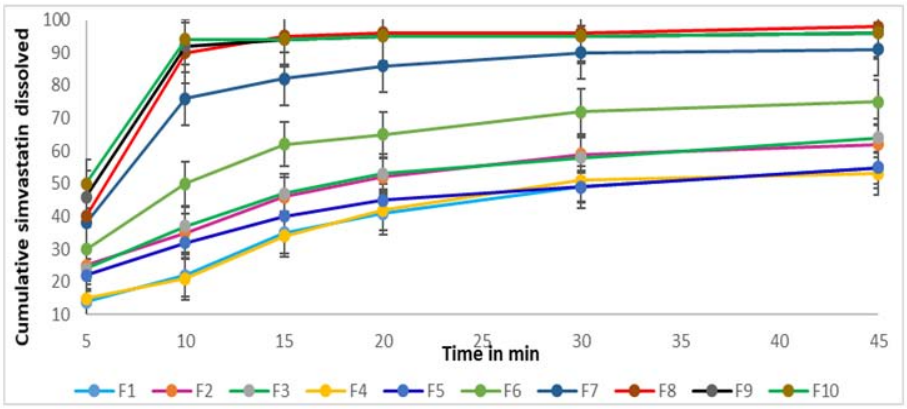

Fig. 3: Dissolution profile of simvastatin from prepared tablets, (All values are reported as mean±standard deviation (SD), n=6)

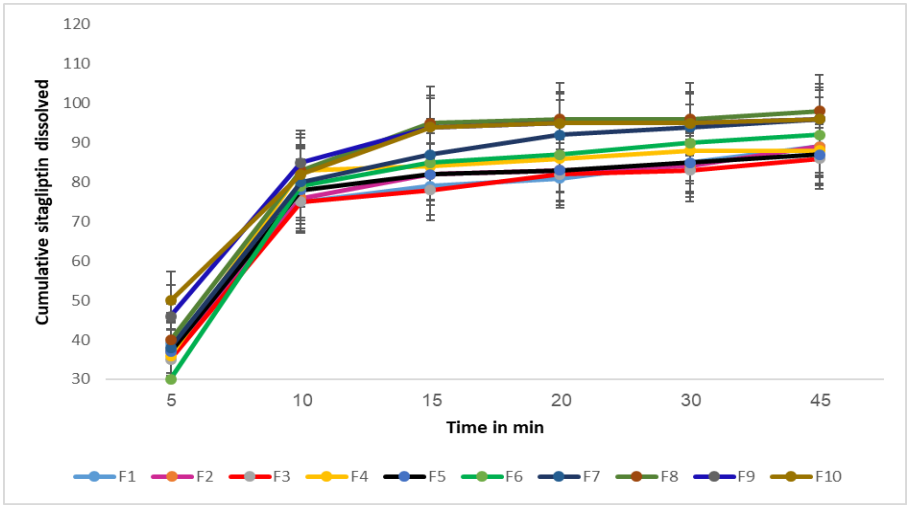

Fig. 4: Dissolution profile of sitagliptin from prepared tablets, (All values are reported as mean±standard deviation (SD), n=6)

CONCLUSION

This study showed a new dosage form of simvastatin and sitagliptin which is rapidly dissolving tablets dosage form. Superdisintegrant addition technique using crospovidone could increase the dissolution of simvastatin and sitagliptin to be more than 90% after 10 min in the formulae F 8, F 9 and F10 prepared with crospovidone in the range of 27-36%, while the dissolution of pure standards of simvastatin and sitagliptin were 12% and 30%, respectively after 10 min showing a great enhancement in the dissolution and the disintegration time was less than 50 sec.

CONFLICT OF INTERESTS

There is no conflict of interest.

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