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Original Article

DESIGN, OPTIMIZATION AND EVALUATION OF EMPAGLIFLOZIN ORODISPERSIBLE TABLETS USING DIFFERENT SUPERDISINTEGRANTS

AKANKSHA DWIVEDI[1,2*], G. N. DARWHEKAR[2]

[1]School of Pharmacy, DAVV, Indore, M. P., India, [2]Acropolis Institute of Pharmaceutical Education and Research, Indore, M. P., India
Email: akd.pharma@gmail.com

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ABSTRACT

Objective: The objective of this study was to formulate orodispersible tablets containing empagliflozin by direct compression method with sufficient hardness and rapid disintegration time and to study the effect of functionality differences of super-disintegrants on the tablet properties.

Methods: A two factor three level factorial design (3^2) was used for the formulation optimization of orodispersible tablets of Empagliflozin and experimental trials were performed on all possible formulations, in which the amount of β-cyclodextrin, crospovidone and croscarmellose sodium were selected as independent variables (factor) varied at three different levels: low (-1), medium (0), and high (+1) levels. The drug release and disintegration time were used as dependent variables (response). All formulations were characterized for parameters such as diameter, hardness, weight, thickness, friability, disintegration time, drug release.

Results: Formulation FD6 having 30 sec disintegration time, 98.84% drug release after 30 min, 2.8 kg/cm^2 hardness and 0.292% friability was found best among all formulations and selected as an optimized formulation with rapid onset of action and enhanced bioavailability (more than 98% drug release within 30 min.) as compared to the oral empagliflozin tablet.

Conclusion: Empagliflozin orodispersible tablets with different superdisintegrants were successfully prepared and formulation containing highest percentage of crospovidone was found best among all other formulations in terms of bioavailability and rapid onset of action.

Keywords: Orodispersible tablet, Empagliflozin, Optimization, Factorial design, Super-disintegrants, Bioavailability

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INTRODUCTION

Among all oral dosage forms; the tablet is most favored because of ease of administration, compactness, and flexibility in manufacturing. In addition, the solid dosage form has the advantage, due to high stability, easy transportation and high precision in administration. However, one of the problems with solid form is dysphagia, which is more common among children, the elderly, and other individuals with nausea and vomiting, aphthous stomatitis due to chemotherapy, Parkinson disease, motion sickness, lack of consciousness, and mental disability [1-4]. The pediatrics and geriatrics patients are of particular concern. To overcome this, orodispersible tablets have been developed. Orodispersible tablets dissolve completely and rapidly. Orodispersible tablets are considered as one of the novel solid dosage forms which turn immediately into liquid in less than a minute and release their drug into the mouth after taking into the mouth and touching saliva. These tablets have had a huge improvement in recent years due to high patient compliance and ease of administration. Orodispersible tablets have the benefits of solid dosage forms and after taking into mouth have the benefits of liquid dosage forms. Moreover, reduction of the first-pass metabolism, rapid onset of action, and higher bioavailability are expected [5-7]. Though, lack of strength and taste masking is of great concern.

The orodispersible tablets prepared by direct compression method, in general, are based on the action established by super disintegrants such as crospovidone and croscarmellose sodium.

Empagliflozin is a sodium glucose co-transporter (SGLT-2) inhibitor that is the new class of oral hypoglycemic agent and indicated as an adjunct to exercise and diet to improve glycemic control in adult patients of type-2 diabetes (non-insulin-dependent diabetes) [8]. The SGLT-2 co-transporters are responsible for reabsorption of glucose from the glomerular filtrate of the kidney, so inhibition of SGLT-2 promotes excretion of blood glucose. Empagliflozin also contributes to reduced hyperglycemia and assists in weight loss and reduction of blood pressure.

It works by stimulating the release of your body's natural insulin. Controlling high blood sugar helps prevent heart disease, strokes, kidney disease, blindness and circulation problems, as well as sexual function problems (impotence). Mechanism of action is produced by blocking potassium K+ channels in beta cells of islets of Langerhans. The increase in calcium will initiate more insulin release from each beta cell. It increases the concentration of insulin in the pancreatic vein. By this, it decreases glucose concentration.

In pharmaceutical field, the β-cyclodextrins are crystalline complexing agents, versatile that have the ability to increase the bioavailability, solubility, and stability of the drug, mask the color and taste of the drugs. In this work solubility of empagliflozin was enhanced by complexing it with β-cyclodextrin.

Since oral absorption of empagliflozin from oral tablet is comparatively poor (takes almost 3 h to get absorbed), hence an effort was made to enhance its absorption by formulating it as the orodispersible tablet. The objective of the present work is to develop orodispersible empagliflozin tablets and to study the effect of functionality differences of super disintegrants on the tablet properties [9]. Orodispersible tablets are gaining prominence as new drug-delivery systems. These dosage forms dissolve or disintegrate in the oral cavity within a minute without the need for water or chewing [10]. The objective of the study was to enhance safety and efficacy of drug molecule to achieve better compliance by solving the problem of difficulty in swallowing, to enhance the onset of action and to provide stable dosage form.

MATERIALS AND METHODS

Empagliflozin was obtained as a gift sample from Novartis Pharmaceuticals (Hyderabad). β-cyclodextrin was purchased from chem. Center, Crospovidone and croscarmellose sodium were purchased from Yarrow Chem Products Ltd. Microcrystalline Cellulose, mannitol, magnesium stearate, talc, methanol, potassium chloride, silica gel G were obtained from Lobachem Pvt. Ltd.

Aspartame, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid were obtained from Merck. All other chemicals and solvents used were of analytical grade.

Prior to formulation preparation, a calibration curve of empagliflozin was prepared in methanol, phosphate buffer pH 6.8 HCl, distilled water and then solubility of empagliflozin was determined in various mediums spectrophotometrically at 221.3 nm using UV-visible spectrophotometer (Shimadzu-1800). The compatibility of the drug was assessed by drug-excipient interaction study. The drug was mixed with various excipients in a 1:1 ratio in glass vials which were properly sealed and labeled and kept undisturbed at 50 °C temperature and 75% RH for 15 d. Physical and chemical observations of all the mixtures were done on the initial day and 15th day by thin layer chromatography (TLC) using silica gel G as stationary phase and toluene: methanol (7:3v/v) as mobile phase [11].

Formulation development

A two factor three level factorial design (3^2) was used for the formulation optimization of the orodispersible tablet of Empagliflozin and experimental trials are performed at all 12 possible formulations, in which the amount of β-cyclodextrin (β-CD), crosspovidone and croscarmellose sodium were selected as independent variables (factor) varied at three different levels: low (-1), medium (0), and high (+1) levels. The drug release and disintegration time were used as dependent variables (response) [12, 13].

10 mg of Empagliflozin with β-CD in the different ratio was taken. β-cyclodextrin was taken in mortar-pestle. Subsequently, drug was incorporated slowly into it and trituration was further continued for one hour and passed through sieve no. # 60 [14-16].

Orodispersible tablets of Empagliflozin were prepared by direct compression method. All the ingredients were weighed accurately according to table 1. All the ingredients were mixed step by step with the drug: β-cyclodextrin inclusion complex and triturated continuously for 15 min. Subsequently, talc and magnesium stearate were mixed and passed through sieve no. #60. The powder was compressed using multi-station tablet punching machine (Aidmach Pvt. Ltd.) with 8 mm flat punch, B-tooling and corresponding die [7-18].

Table 1: Composition of different empagliflozin orodispersible tablets

S. No.	Ingredients	FD 1 (mg)	FD 2 (mg)	FD 3 (mg)	FD 4 (mg)	FD 5 (mg)	FD 6 (mg)	FD 7 (mg)	FD 8 (mg)	FD 9 (mg)	FD 10 (mg)	FD 11 (mg)	FD 12 (mg)
1.	Drug (Empagliflozin)	10	10	10	10	10	10	10	10	10	10	10	10
2.	β-cyclodextrin	10	10	10	20	20	20	10	10	10	20	20	20
3.	Crospovidone	7.5	10	12.5	7.5	10	12.5	-	-	-	-	-	-
4.	Croscarmellose sodium	-	-	-	-	-	-	7.5	10	12.5	7.5	10	12.5
4.	Microcrystalline cellulose	130	130	130	130	130	130	130	130	130	130	130	130
5.	Mannitol	40	40	40	40	40	40	40	40	40	40	40	40
6.	Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
7.	Magnesium Stearate	4	4	4	4	4	4	4	4	4	4	4	4
8.	Talc	6	6	6	6	6	6	6	6	6	6	6	6

Precompression parameters of powder

Bulk density

This was calculated by using the formula:

Bulk density = Weight of the sample/Bulk volume of the powder

Tapped density

Tapped density was calculated by using the following formula:

Tapped density = Weight of the sample/Tapped volume of powder

Carr's index

Carr's index of the powder blend was determined by using the formula:

$$\text{Carr's index (\%) I} = [(V0 - Vt) \div V0] \times 100$$

Where, Vo = Tapped density of powder,

Vt =Bulk density of powder

Angle of repose

The angle of repose was calculated by measuring the diameter and height of powder cone and putting the values to the following equation.

$$\theta = tan^{-1} \quad (h/r)$$

Where h= height of the cone.

r = radius of the cone.

Hausner's ratio

It was calculated by following formula**:**

Hausner's ratio = Tapped density/Bulk density [19-21]

Evaluation of inclusion complex

Solubility determination

An excess amount of prepared Empagliflozin: β-cyclodextrin inclusion complex at different concentration (1:1, 1:2) were separately dissolved in 5 ml phosphate buffer pH 6.8 in vials and sealed properly and stirred continuously at 37 °±2 °C. The process was repeated until saturation-solubility of inclusion complex. The solution was kept for 24 h at room temperature. The solution was filtered and adequately diluted with phosphate buffer pH of 6.8. The solution was analyzed using UV-visible spectrophotometer at 221.3 nm [22].

Post compression parameter of orodispersible tablets

Physical characterization

All the batches were evaluated for weight variation, hardness, friability, thickness as per IP. The weight variation was determined by taking 20 tablets using electronic balance. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester. Friability was determined by testing 20 tablets in a Roche friability tester for 4 min at 25 rpm.

***In vitro* disintegration time**

In vitro disintegration time was performed according to the monograph of IP. The six tablets for determining the disintegration time were placed in each tube of the disintegration test apparatus and the time required for the disintegration of each tablet was measured at 37±0.5 °C using 900 ml distilled water.

Drug content

Ten tablets were taken and the amount of drug present in each formulation of the tablet was determined. The tablet was crushed in a mortar-pestle and equivalent to 10 mg of drug was dissolved in phosphate buffer pH 6.8 in a 100 ml volumetric flask. Volume was made up to 100 ml. The sample was filtered through filter paper.

From this solution 1 ml was taken in a 10 ml volumetric flask and diluted with phosphate buffer pH 6.8. Further, 1 ml was taken and diluted up to 10 ml and analyzed for drug content by UV spectrophotometer at 221.3 nm using phosphate buffer (pH 6.8).

Wetting time and water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish containing 10 ml of water. A tablet was put on the tissue paper and the time required for the water to diffuse from the wetted absorbent paper throughout the tablet was then recorded using a stopwatch.

For water absorption ratio

The wetted tablets were reweighed. The water absorption ratio R was determined using the following equation

$$R = 100 \times (Wa - Wb)/Wb$$

Where, Wa = Weight of the tablet after water absorption

Wb = Weight of the tablet before water absorption [23-24]

***In vitro* drug release study**

In vitro drug release study was determined by dissolution test apparatus. The water level was maintained in the water bath up to the specific mark and 900 ml of phosphate buffer pH 6.8 was poured in dissolution vessel. The tablets were put in each vessel and paddle was allowed to rotate at 50 rpm for 30 min and the temperature was maintained at 37±0.5 °C. At the definite time intervals 5, 10, 15, 20, 25, 30 min the aliquots of the dissolution medium (5 ml) were withdrawn and the same volume of the medium (6.8 pH phosphate buffer) was replaced to maintain the sink condition. The samples were analyzed for drug release by UV-visible spectrophotometer at λ max 221.3 nm using phosphate buffer pH 6.8 as blank.

At the same time *in vitro* drug release data of formulated optimized orodispersible tablet was compared with the marketed oral empagliflozin tablet.

RESULTS AND DISCUSSION

Table 2: Absorbance data of Empagliflozin in methanol for preparation of the calibration curve at 221.3 nm

S. No.	Concentration(µg/ml)	Absorbance*
1	2	0.112±0.009
2	4	0.210±0.007
3	6	0.323±0.013
4	8	0.428±0.018
5	10	0.526±0.012

***** All data are given in mean±SD, n=3

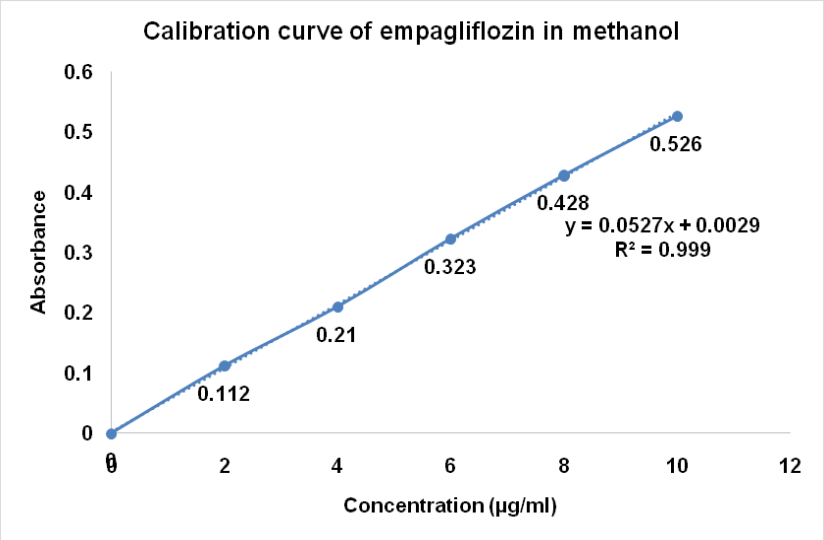

Fig. 1: Calibration graph of Empagliflozin in methanol at 221.3 nm, empagliflozin in methanol follows the Beer–Lambert's law in the concentration range of 2-10 µg/ml

Table 3: Absorbance data of Empagliflozin in phosphate buffer pH 6.8 for preparation of the calibration curve at 221.3 nm

S. No.	Concentration (µg/ml)	Absorbance*
1	2	0.102±0.002
2	4	0.203±0.001
3	6	0.311±0.001
4	8	0.423±0.002
5	10	0.503±0.002

*All data are given in mean±SD, n=3

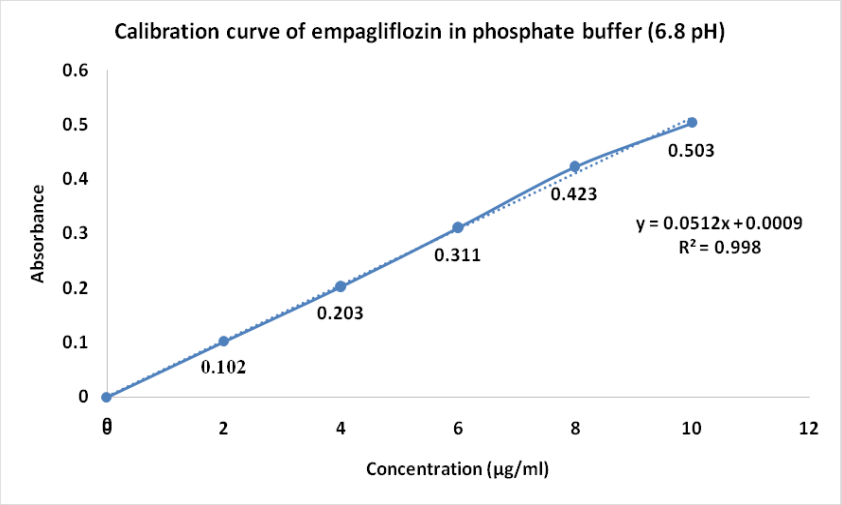

Fig. 2: Calibration graph of Empagliflozin in phosphate buffer pH 6.8 at 221.3 nm, Empagliflozin in phosphate buffer pH 6.8 follows the Beer–Lambert's law in the concentration range of 2-10 µg/ml

Table 4: Absorbance data of Empagliflozin in pH 1.2 HCl for preparation of the calibration curve, at 221.3 nm

S. No.	Concentration (µg/ml)	Absorbance*
1	2	0.097±0.002
2	4	0.195±0.002
3	6	0.264±0.002
4	8	0.357±0.004
5	10	0.427±0.004

* All data are given in mean±SD, n=3

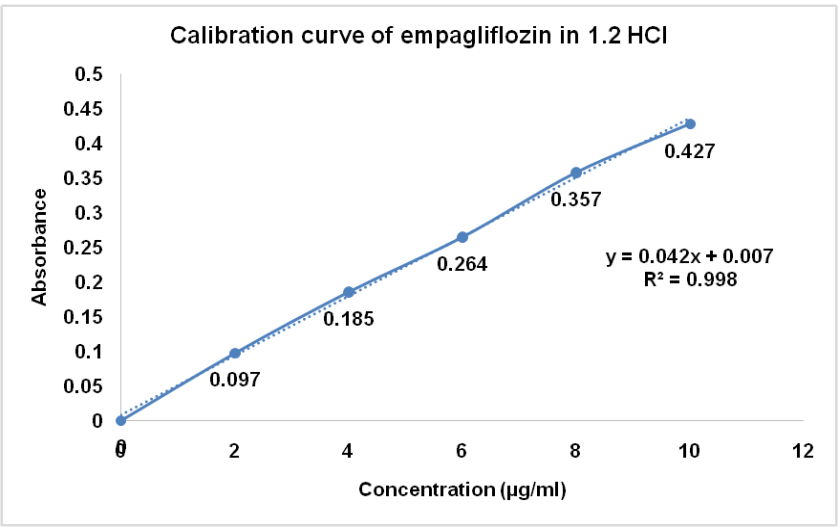

Fig. 3: Calibration graph of Empagliflozin in pH 1.2 HCl buffer at 221.3 nm, empagliflozin in pH 1.2 HCl follows the Beer–Lambert's law in the concentration range of 2-10 µg/ml

Table 5: Absorbance data of Empagliflozin in distilled water for preparation of the calibration curve, at 221.3 nm

S. No.	Concentration (µg/ml)	Absorbance*
1	2	0.089±0.001
2	4	0.155±0.003
3	6	0.216±0.002
4	8	0.295±0.001
5	10	0.374±0.001

*All data given in mean±SD, n=3

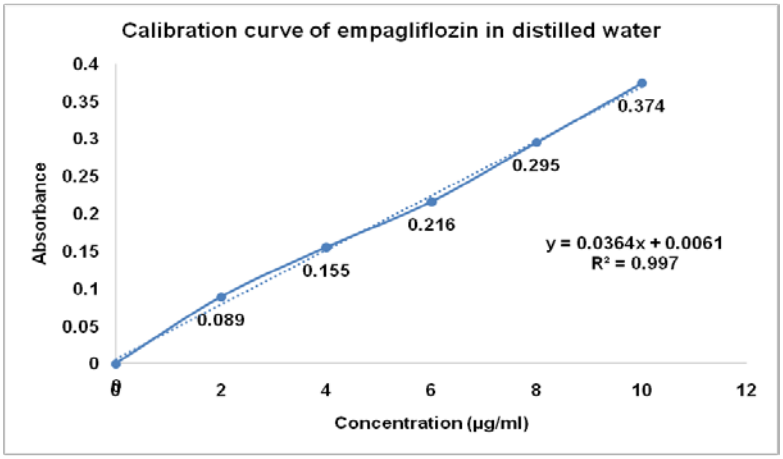

Fig. 4: Calibration graph of empagliflozin in distilled water at 221.3 nm, empagliflozin in distilled water follows the beer–lambert's law in the concentration range of 2-10 µg/ml

Determination of solubility of Empagliflozin in various medium

Table 6: Solubility data of Empagliflozin in different mediums

S. No.	Solvent	Solubility (mg/ml)*
1	Methanol	46.318±0.869
2	Phosphate buffer pH 6.8	0.394±0.002
3	pH 1.2 HCl buffer	0.305±0.017
4	Distilled water	0.106±0.002

*All data are given in mean±SD, n=3

Determination of solubility of inclusion complex

Table 7: Solubility data of inclusion complex

S. No.	Phosphate buffer pH 6.8	Solubility (mg/ml)*
1	Pure drug	0.394±0.002
2	Drug: β-CD (1:1)	8.361±0.007
3	Drug: β-CD (1:2)	11.525±0.006

*data are given in mean±SD, n=3

Drug-excipient interaction study

The drug (Empagliflozin) was found to be compatible with various excipients which were selected for the formulation of the orodispersible tablet. The compatibility was assessed by TLC and the retention factors of all ratios found similar.

Evaluation of precompression parameters of powder

The bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose of selected formulations were performed and shown in table no.7.8. The results show that all formulations that possess a good flow property.

Evaluation of post-compression parameters of orodispersible tablet

The orodispersible tablet of Empagliflozin was evaluated for weight variation, hardness, thickness, friability, disintegration time, drug content, wetting time and water absorption ratio. The results of the studies were shown in the below table:

***In vitro* drug release study of orodispersible tablet**

The percentage cumulative drug release from formulations FD1 to FD12 was determined. The formulation FD6 showed the highest release (%) within 30 min.

Table 8: Data of drug-excipient interaction study

S. No.	Drug/drug+excipient ratio (1:1)	Physical appearance (initial)	Present day (Rf)	Physical appearance (final)	After15 d (Rf)	Inference
1.	Drug (Empagliflozin)	White	0.54	White	0.54	No Change
2.	Pure Drug+β-cyclodextrin	White	0.51	White	0.52	No Change
3.	Pure Drug+Crospovidone	White	0.52	White	0.53	No Change
4.	Pure Drug+Croscarmellose Sodium	White	0.55	White	0.56	No Change
4.	Pure Drug+MCC	White	0.53	White	0.54	No Change
5.	Pure Drug+Mannitol	White	0.49	White	0.50	No Change
6.	Pure Drug+Aspartame	White	0.56	White	0.56	No Change
7.	Pure Drug+Magnesium stearate	White	0.57	White	0.58	No Change
8.	Pure Drug+Talc	White	0.54	White	0.53	No Change
9.	Pure drug+Mixture	White	0.53	White	0.55	No Change

Table 9: Evaluation of precompression parameters of powder

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
FD1	0.278±0.001	0.322±0.001	13.544±0.882	1.15±0.010	30.18±0.759
FD2	0.302±0.004	0.353±0.003	14.513±0.972	1.16±0.015	29.21±0.298
FD3	0.321±0.003	0.366±0.003	11.845±0.634	1.13±0.005	28.45±0.796
FD4	0.327±0.003	0.383±0.003	14.692±1.112	1.16±0.015	27.88±0.904
FD5	0.344±0.002	0.389±0.003	11.642±0.185	1.12±0.005	26.74±0.767
FD6	0.356±0.004	0.405±0.004	11.243±0.275	1.12±0.005	25.81±0.260
FD7	0.272±0.003	0.314±0.002	13.252±1.062	1.14±0.015	31.22±0.498
FD8	0.285±0.002	0.337±0.002	15.590±1.376	1.18±0.020	29.47±0.726
FD9	0.304±0.002	0.352±0.003	13.616±1.465	1.15±0.020	29.56±0.647
FD10	0.315±0.002	0.376±0.003	16.370±0.359	1.19±0.005	28.89±0.847
FD11	0.334±0.004	0.396±0.003	15.643±0.677	1.18±0.011	28.91±0.481
FD12	0.355±0.003	0.414±0.003	14.389±0.293	1.16±0.005	26.86±0.678

* All data are given in mean±SD, n=3

Table 10: Weight variation, hardness, thickness, and friability of formulation FD1-FD12

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)
FD1	217.1±1.351	3.58±0.095	2.5±0.115	0.445±0.015
FD2	219.8±3.305	3.63±0.037	2.6±0.152	0.292±0.017
FD3	222.2±4.416	3.67±0.028	2.6±0.057	0.309±0.015
FD4	227.4±2.450	3.70±0.032	2.6±0.1	0.413±0.016
FD5	230.2±1.503	3.71±0.031	2.7±0.057	0.310±0.008
FD6	232.2±1.665	3.78±0.055	2.8±0.057	0.292±0.015
FD7	217.2±2.650	3.61±0.070	2.5±0.057	0.382±0.015
FD8	220.3±1.435	3.64±0.049	2.6±0.1	0.315±0.019
FD9	222.3±3.450	3.69±0.040	2.7±0.115	0.329±0.013
FD10	227.3±4.360	3.74±0.055	2.6±0.152	0.405±0.011
FD11	229.9±1.493	3.73±0.050	2.7±0.152	0.384±0.015
FD12	232.4±1.404	3.75±0.050	2.7±0.057	0.294±0.005

*All data given in mean±SD, n=3

Table 11: Disintegration time, drug content, wetting time and water absorption ratio of formulation FD1-FD12

Formulation	Disintegration time (sec)	Drug content (%)	Wetting time (sec)	water absorption ratio (%)
FD1	38.02±0.569	95.69±0.774	33.97±0.437	60.17±0.196
FD2	39.44±0.559	96.48±0.672	36.34±0.646	58.60±1.257
FD3	31.52±0.597	98.49±0.772	41.67±0.308	55.75±1.863
FD4	34.59±0.299	96.65±0.447	44.21±0.259	58.30±1.305
FD5	37.15±0.577	97.58±0.668	32.21±0.219	56.10±0.578
FD6	30.56±0.370	99.37±0.498	30.11±0.696	53.15±0.204
FD7	33.02±1.115	95.17±0.596	45.43±0.591	59.30±0.386
FD8	34.82±0.488	96.51±0.057	35.33±0.249	57.76±0.357
FD9	32.33±0.3	98.33±0.847	34.02±0.488	54.69±0.430
FD10	35.77±0.691	94.43±0.651	32.56±0.14	58.9±1.225
FD11	36.20±0.537	97.53±0.951	35.50±0.186	55.2±0.420
FD12	31.40±0.549	99.06±0.908	38.05±0.091	54.60±1.230

*All data are given in mean±SD, n=3

Table 12: Percentage cumulative drug release data of FD1 to FD6 formulation of orodispersible tablets using "Crospovidone" as super-disintegrant

Time (in min)	% Cumulative drug Release					
	FD1	FD2	FD3	FD4	FD5	FD6
0	0	0	0	0	0	0
5	21.74±0.489	24.91±1.497	25.20±0.809	22.95±0.537	24.30±0.839	26.54±0.991
10	40.61±0.587	41.37±0.566	49.63±1.201	31.34±0.809	34.97±0.567	36.01±0.546
15	51.68±0.609	53.59±0.829	54.03±1.887	41.09±1.417	43.72±0.546	49.94±0.459
20	60.5±0.786	68.45±0.635	72.5±0.695	53.96±0.546	60.8±0.668	63.57±0.587
25	71.4±0.769	79.98±1.56	84.06±0.236	72.36±0.608	76.7±0.739	81.29±1.207
30	85.09±0.954	93.85±0.819	95.23±1.569	80.25±0.776	92.3±0.728	98.84±0.618

*All data given in mean±SD, n=3

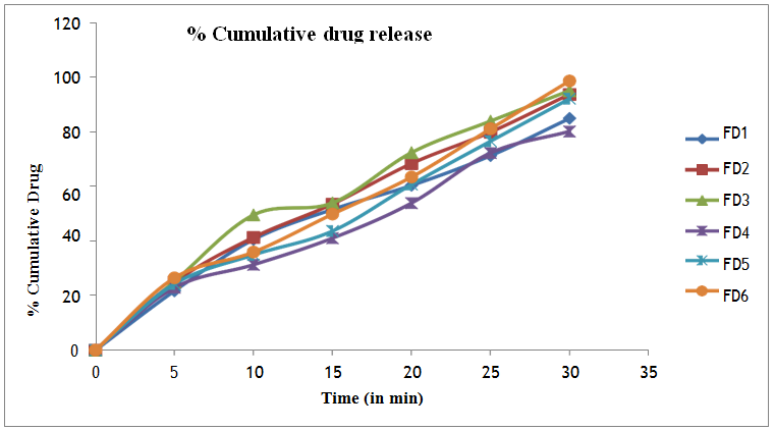

Fig. 5: Percentage cumulative drug release graph from formulation FD1-FD6

Table 13: Percentage cumulative drug release data of FD7 to FD12 formulation of orodispersible tablets using "Croscarmellose sodium" as super-disintegrant

Time (in min)	% Cumulative drug release					
	FD7	FD8	FD9	FD10	FD11	FD12
0	0	0	0	0	0	0
5	19.47±0.207	20.36±0.896	22.74±0.601	21.23±0.926	24.94±0.567	26.41±0.762
10	26.97±0.577	33.77±0.828	34.37±0.579	30.35±0.706	31.74±1.126	35.79±0.697
15	42.79±0.989	48.67±0.667	56.98±1.966	42.58±0.496	49.56±0.556	59.74±0.346
20	66.97±1.112	68.49±0.809	79.36±0.617	59.27±1.463	70.18±0.147	74.20±0.209
25	72.40±2.307	82.39±1.226	86.27±0.563	76.29±0.455	82.01±0.307	89.84±0.465
30	86.5±1.336	90.45±0.129	97.94±0.337	88.05±0.639	96.14±0.559	98.59±0.957

***** All data are given in mean±SD, n=3

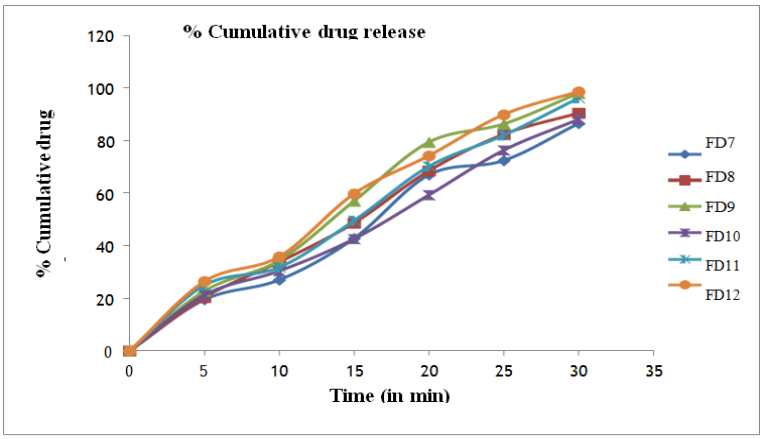

Fig. 6: Percentage cumulative drug release graph from formulation FD7-FD12

Evaluation of precompression parameters of powder of optimized tablet (FD6)

The bulk density, tapped density, Carr's index, angle of repose and Hausner's ratio of optimized formulations ware performed and shown in table no. 14. All the results show that the optimized formulations possess a good flow property.

Evaluation of post-compression parameters of optimized tablet (FD6)

The orodispersible tablet of Empagliflozin was evaluated like weight variation, hardness, thickness, friability, and disintegration time, drug content, wetting time and water absorption ratio and *in vitro* drug release study. The results of the study were shown in below table:

Table 14: Evaluation of precompression parameters of powder of optimized tablet (FD6)

Formulation Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (o)
FD6	0.356±0.004	0.405±0.004	11.243±0.275	1.12±0.005	25.81±0.260

*All data are given in mean±SD, n=3

Table 15: Weight variation, hardness, thickness, and friability of formulation FD6

Formulation Code	Weight variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)
FD6	232.2±1.665	2.8±0.057	3.78±0.055	0.292±0.015

*All data are given in mean±SD, n=3

Table 16: Disintegration time, drug content, wetting time and water absorption Ratio, and of optimized tablet (FD6)

Formulation code	Disintegration time (sec)	Drug content (%)	Wetting time (sec)	Water absorption ratio (%)
FD6	30.56±0.370	99.37±0.498	30.11±0.696	53.15±0.204

*All data are given in mean±SD, n=3

***In vitro* drug release study of the orodispersible tablet (FD6)**

The percentage cumulative drug release from formulations (FD6) was found to be approximately 98% within 30 min.

Table 17: Percentage cumulative drug release data of optimized tablet (FD6)

S. No.	Time (in min)	% Cumulative drug release Optimized formulation
1	0	0.0±0.0
2	5	26.54±0.991
3	10	36.01±0.546
4	15	49.94±0.459
5	20	63.57±0.587
6	25	81.29±1.207
7	30	98.84±0.618

*All data are given in mean±SD, n=3

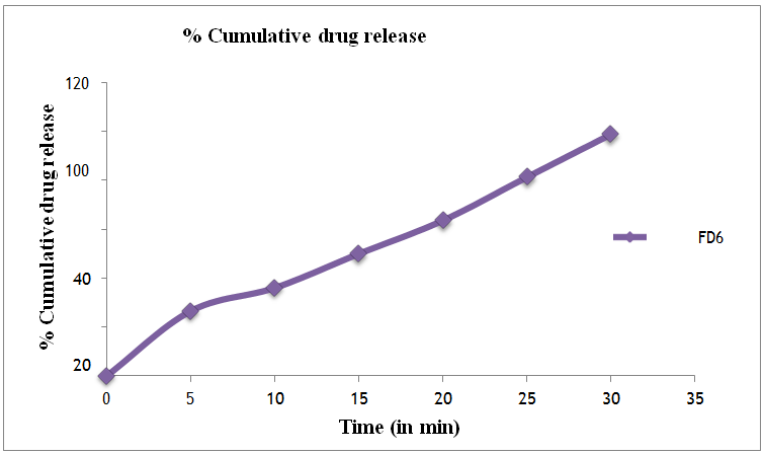

Fig. 7: Percentage cumulative drug release graph of optimized orodispersible tablet FD6

Table 18: Percentage cumulative drug release data of marketed empagliflozin oral tablet

S. No.	Time (min)	% Cumulative drug release Marketed empagliflozin formulation
1	0	0.0±0.0
2	30	19.33±0.012
3	60	39.38±0.422
4	90	52.41±0.740
5	120	70.09±0.005
6	150	82.64±0.072
7	180	98.05±0.800

*All data are given in mean±SD, n=3

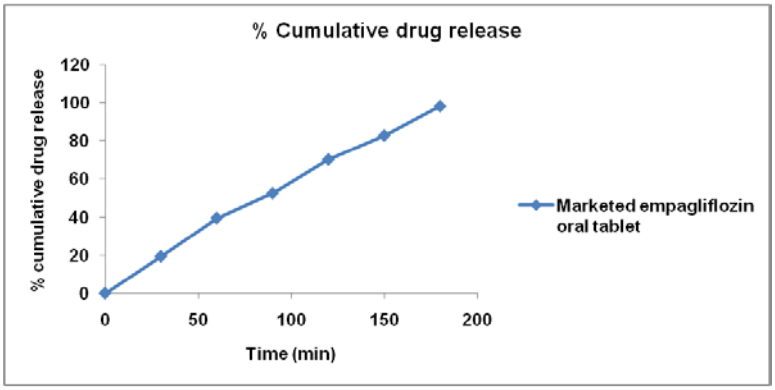

Fig. 8: Percentage cumulative drug release graph of marketed empagliflozin oral tablet

DISCUSSION

In this work, we have attempted to enhance the solubility of empagliflozin in aqueous media by making the inclusion complex. The FDTs were prepared by direct compression method. Empagliflozin orodispersible tablets were prepared by direct compression method using different super-disintegrants (crospovidone and croscarmellose sodium) and other excipients. A total number of 12 formulations were prepared by direct compression method. The pre-formulation studies such as bulk density, tapped density, the angle of repose, compressibility index and Hausner ratio were evaluated. All the data obtained from physicochemical parameters such as hardness, friability, and weight variation, drug content, wetting time, disintegration time, dispersion time and *in vitro* drug dissolution are found within limits. Results showed that crospovidone has greater super-disintegration power as compared to croscarmellose sodium in the same percentage (12.5%) for orodispersible tablets [25]. Therefore out of all formulations, F6 was found satisfactory in terms of rapid onset of action, enhanced absorption as compared to the marketed oral empagliflozin tablet.

CONCLUSION

The present research work envisages the applicability of super-disintegrants such as crospovidone and croscarmellose sodium in the design and development of orodispersible tablets of Empagliflozin utilizing the (3^2) factorial design.

In the present work solubility of the drug was enhanced by using inclusion complex. The formulations prepared using direct compression, were evaluated for precompression parameters which were found to be within limits. The increased concentration of the super-disintegrants enhanced the porosity of the tablet, due to which it reduced the disintegration time and wetting and maximum drug release in 30 min. Compressed tablets were evaluated for post-compression parameters which were found to be good. From all the results it is concluded that formulation FD6 containing crospovidone was found to be the best formulation in terms of flow property, disintegration time (30.5 sec),, wetting time (30.1 sec), drug content and maximum percentage drug release 98.8% within 30 min. Thus, the present study demonstrated the potential of the formulated orodispersible tablets for rapid absorption, improved bioavailability, effective therapy, and improved patient compliance by defeating all the problems of swallowing as compared to the oral empagliflozin tablets.

AUTHORS CONTRIBUTIONS

Both authors contributed equally in the designing, conducting and preparation of the manuscript of this research work.

CONFLICT OF INTERESTS

No conflicts of interest associated with this work

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