The Pharma Innovation Journal 2018; 7(3): 202-207

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(3): 202-207

www.thepharmajournal.com
Received: 01-01-2018
Accepted: 02-02-2018

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Development, characterization and evaluation of empagliflozin spherical agglomerates using spherical agglomeration technique

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Abstract
The present research work embodies the preparation of spherical agglomerates of empagliflozin with increased solubility, flow and compression properties using novel crystallization technique. The drug was dissolved in 30ml dichloromethane (good solvent) and stirred. 100ml of water (poor solvent) was added and continued stirring. 5ml of chloroform (bridging liquid) was added and stirred at 1000rpm for 40minutes to precipitate empagliflozin. The precipitated particles were filtered and dried at 40 °C. Spherical agglomerates were characterized by IR spectroscopy, X-ray diffraction studies, DSC and SEM and its results showed that no physical or chemical interaction existed in the prepared agglomerates. A Fourier transform infrared (FTIR) study indicated compatibility of drug with the excipients. The agglomerates can be made directly into tablets because of their excellent flowability. Directly compressed tablets of the Empagliflozin agglomerates exhibited hardness, friability and weight variation appropriately along with improved drug release characteristics. Among the different control release polymers Caesalpinia spinosa (natural mucoadhesive polymer) showed increased drug release retarding capacity. F3 showed the satisfactory results and have better sustainability. The developed agglomerates were spherical with smooth surface and dissolution profile was faster and exhibited improved solubility along with proper micromeritic properties than pure drug. The significantly improved micromeritic properties compared to the plain drug suggested its suitability for direct compression.

Keywords: Spherical Agglomerates, Caesalpinia spinosa, HPMC, Ethyl Cellulose, Empagliflozin

Introduction
Formulation and manufacture of solid oral dosage forms, and tablets especially, have undergone rapid change and development over the last several decades. One of the most revolutionary technologies is that of direct compression. In direct tabletting method, it is necessary to increase flowability and compressibility of the bulk powder inorder to retain a steady supply of powder mixture to the tabletting machine and sufficient mechanical strength of the compacted tablets [1].

Development of novel methods to improve the bioavailability of poorly soluble drugs is a big challenge to formulate solid dosage form. Spherical agglomeration is one of such techniques to improve the micromeritic properties and dissolution of the drug. Spherical agglomeration is a process of formation of aggregates of crystals held together by liquid bridges. The agglomerates are formed by agitating the crystals in a liquid suspension in presence of binding agent [2]. It is the latest technique of enlarging smaller particles of solid into large size by inter-particle agglomeration [3, 4]. This technique can also be exploited to increase solubility, dissolution and hence bioavailability of poorly soluble drugs [5-7].

Diabetes mellitus is a serious and chronic metabolic disease that is characterized by high blood glucose (hyperglycemia) and affects millions of people worldwide. SGLT2 is a Sodium-dependent Glucose co-Transporter protein, which affects the reabsorption of glucose in the kidney. It is estimated that 90% of renal glucose reabsorption is facilitated by SGLT2. Since glucose reabsorption is mediated predominantly by SGLT2 and because high glucose levels have been identified as a cause of disease in diabetes, SGLT2 has become a drug target for type 2 diabetes therapy. Selective inhibition of SGLT2 has the potential to reduce hyperglycemia by inhibiting glucose reabsorption in the kidney with elimination of glucose by excretion in the urine (glucosuria). Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of diabetic medications indicated only for the treatment of type 2 diabetes [8].

Polymers like HPMC K100M (hydrophilic polymer), caesalpinea spinosa (natural polymer), Ethyl cellulose were used with different viscosity grades.

Materials and Methods

Empagliflozin drug was obtained as a gift sample from Laurus labs Private Limited, Hyderabad. Ethyl cellulose was obtained as a gift sample from Astra Zeneca Bangalore, India. All other chemicals used were of pharmacopeial grade. All solvents employed in this research were of analytical grade and utilized as such procured.

Extraction of Natural Mucoadhesive Material from Caesalpinea Spinosa

Collection and authentication of plant

The seeds of caesalpinea spinosa were collected from in and around areas of Nellore disctrict. The plants were authenticated by Prof. K. Madhava Chetty, Department of Botany, SV University, Tirupathi, Chittoor District, Andhra Pradesh and seeds specimen samples were kept in the laboratory for further use.

Caesalpinia spinosa, a small tree belonging to the family Leguminosae. Commonly known as Tara, which is a gum obtained from the seed (endosperm) of Caesalpinia spinosa. The Tara gum is an odorless, white powder. It is obtained by removing and grinding the endosperm of the mature black colored seeds of Tara plant. The primary component of the gum is a galactomannan polymer similar to the main constituents of guar and locust bean gums. In various pharmaceutical and food industries, Tara gum is used as a thickening agent and a stabilizer around the world. Further studies also gave an idea about its applications in various patents like; the use of tara gum as a controlled release formulations includes a gastro retentive controlled drug delivery systems and used as emulsions for various drug products [8-11].

Extraction of natural mucoadhesive materials

The collected seeds were washed thoroughly with water to remove the adhering materials. 500gm of dried seeds were soaked in distilled water (2500ml) separately for 24 hr and later boiled for one hour with continuous stirring at 2000rpm and then kept aside for the release of natural gum into water. The soaked seeds were then squeezed using multiple folds of muslin cloth to separate the marc from the filtrate. The marc was not discarded but it was used for multiple or several extractions. All the extractions were pooled and concentrated under vaccum at 60C to half of the volume. Then to the filtrate equal quantity of acetone was added to precipitate the natural mucoadhesive material, which was later separated by filtration. The precipitated mucilage was dried at 60C in a hot air oven. The dried mucoadhesive agent was powdered, passes through the sieve no.100 and is stored in an airtight container at room temperature for further use. This natural mucoadhesive material is used for different formulations.

Physical Characterization of Spherical Agglomerates

Differential scanning calorimetry (DSC) study

A DSC study was carried out to determine possible polymorphic transitions during the crystallization procedure. DSC measurements were performed with a thermal analyser [12-16].

FT-IR Spectroscopy

The FT-IR spectral data were measured at ambient temperature using a Shimadzu, model 8033(USA). Samples were dispersed in KBr powder and pellets were made by applying 5 ton pressure [12-16].

X-RAY Analysis

X-Ray powder diffraction studies were obtained at room temperature using Bruker diffractometer, with Cu acting as anode material and graphite monochromator, operated at an voltage of 40mA, 45kV [12-18].

Scanning Electron Microscopy (SEM)

SEM (Shimadzu-LV-5600, USA) photographs were obtained inorder identify and confirm spherical character and surface topography of the crystals [12-18].

Drug content

Drug content was determined by taking spherical agglomerates of empagliflozin equivalent to 100mg empagliflozin were triturated and dissolved in a solvent mixture containing dichloromethane: water: chloroform(30:100:5 v/v). Diluted samples were filtered from 0.45µ injection filter and the drug content was determined spectrophotometrically at 272nm using UV-Visible spectrophotometer (Lab india, UV 3000+)

Yield and Micromeritic properties

The yield of prepared agglomerates were determined by the weight of agglomerates after drying. Bulk density (sisco), tapped density was determined by tap density tester and carr´s index and hausners ratio were determined. The flow behaviour of raw crystals and spherical agglomerates was characterized by angle of repose by using fixed funnel method.

Preparation of Empagliflozin Tablets

Empagliflozin was dissolved in 30ml dichloromethane and stirred 100ml water was added and continued stirring. 5ml of chloroform was added and stirred at 1000rpm for 40min to precipitate the drug. The precipitated recrystallized agglomerates were collected by vaccum filtration and dried in oven at 40 °C for 6hr. The dried crystals were stored in dessicators at room temperature prior to use. The above procedure was repeated several times to obtain enough materials for characterization and to observe repetability. Formulation codes were given for spherical agglomerates with polymers (ceasalpinea spinosa, HPMC, ethyl cellulose) from F1 to F9 and for pure drug with polymers from F10 to F18 respectively.

Empagliflozin agglomerates equivalent to 10mg of Empagliflozin were mixed manually with directly compressible microcrystalline cellulose and the blend was finally mixed with magnesium stearate for 2 min. Final blend (150mg per tablet) was compressed by using rotary tablet machine with 6mm standard concave punch. Hardness, thickness, friability of tablets were studied by Monsanto Hardness tester, vernier calipers (Cd 6”Cs), Roche friabilator (ELECTRO LAB) respectively. The weight variation of the tablets was determined taking weight of 20 tablets using electronic balance.

Evaluation of Empagliflozin tablets *in vitro* dissolution study

The dissolution profile of raw crystals and spherical agglomerates of empagliflozin were performed by using USP 26 type II dissolution test apparatus (electro lab 08L) in 900ml of pH 7.5 phosphate buffer. Temperature was maintained at 37±2 °C and 50rpm stirring was provided for every dissolution study. At predetermined time intervals, 5ml

of samples were withdrawn and analysed spectrophotometrically. At each time of withdrawl, 5ml of fresh corresponding medium was replaced into the dissolution flask. Upon filtration through Whattman filter paper, concentration of empagliflozin was determined spectrophotometrically at 272nm [12-18].

Results and Discussion

FT-IR Spectra of Empagliflozin

Empagliflozin pure drug & Empagliflozin spherical agglomerates

Specific changes in IR spectra are not clear, could be due to variations in resonance structure, rotation of a part of a molecular or certain bonds. Empagliflozin, physical mixture of the excipients, and the physical mixture of drug with excipients were separately mixed with potassium bromide at a ratio of 1:100, and the pellets were prepared by applying 10 metric ton of pressure using a hydraulic press. The FTIR spectra were recorded for the samples over a range of 4000–400 cm^{-1} using the FTIR instrument.

X-RAY Diffraction spectra of Empagliflozin

All the drug samples exhibited similar peak positions in X-ray diffraction studies. X-ray diffraction (XRD) study was performed to evaluate changes, if any, in the crystalline nature of the drug. Powder XRD analysis was performed for Spherical Agglomerates and pure drug using an X-ray diffractometer. The samples were irradiated with the monochromatized CuKα radiation and analyzed at 2° theta.

DSC Results

The DSC thermograms shows a sharp endothermic peak for all the empagliflozin crystals. Five milligrams of samples were scanned from 20 °C to 300 °C under inert nitrogen atmosphere at a heating rate of 10 °C/min using a Shimadzu thermal analyzer (Shimadzu DSC-60, TA-60, Japan).

Scanning electron microscopy of Empagliflozin

Crystals of pure sample are of smallest size and have irregular shapes. Recrystallization product crystals have intermediate size. The agglomerates were formed by coalescence of the microcrystalline precipitates, so the agglomerates had a rugged surface. Agglomerates obtained were spherical in its shape. For studying of the surface morphology by SEM, the samples were attached to sample stubs, silver-coated, and viewed using an accelerating voltage at the magnification of ×15,000.

Dissolution profiles

The dissolution profile of empagliflozin showed remarkable dissolution behavior for spherical agglomerates than pure drug. Prepared spherical crystals exhibited decreased crystallanity and improved micromeritic properties. Amount of bridging liquid, speed of agitation and duration of agitation had its effect on the mechanical and micromeritic properties of spherical crystals. DSC results further supported IR spectroscopy results, which indicated the absence of any interactions between drug and additives used in the preparation. Hence the spherical crystallization technique can be used for formulation of tablets of empagliflozin by direct compression with directly compressible excipients. On the other hand, all prepared spherical agglomerates exhibited good compressibility indicating good packability. Among the different control release polymers Caesalpinia spinosa showed highest drug release retarding capacity. F3 was showing the satisfactory results and having better sustainability. When we plot the release rate kinetics for best formulation f3 was following zero order release.

Acknowledgements

The authors are thankful to Saastra college of pharmaceutical education and research, Nellore for providing research grant for this project. The authors are also thankful to Laurus labs Private Limited, Hyderabad, India, for providing free gift sample of Empagliflozin and also thankful for Astra Zeneca Bangalore, India for proving free gift samples of HPMC and ethyl cellulose.

Table 1: Formulation chart

	Spherical Agglomerates of Empagliflozin									Empagliflozin API								
Ingredients(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
Drug	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
mccph112	128.5	118.5	108.5	128.5	118.5	108.5	128.5	118.5	108.5	128.5	118.5	108.5	128.5	118.5	108.5	128.5	118.5	108.5
caesalpinia spinosa	10	20	30	-	-	-	-	-	-	10	20	30	-	-	-	-	-	-
hpmck100m	-	-	-	10	20	30	-	-	-	-	-	-	10	20	30	-	-	-
ethyl cellulose	-	-	-	-	-	-	10	20	30	-	-	-	-	-	-	10	20	30
mg sterate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150

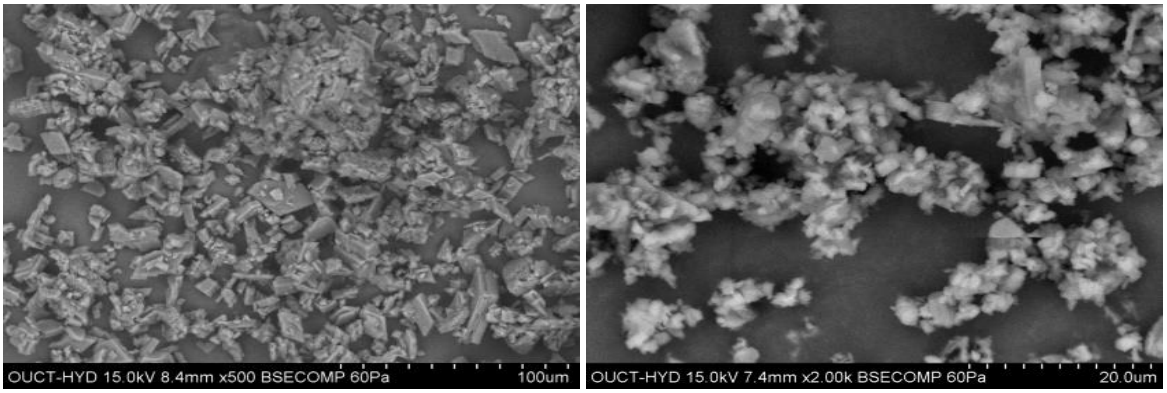

Fig 1: Scanning Electron Microscopy of Empagliflozin

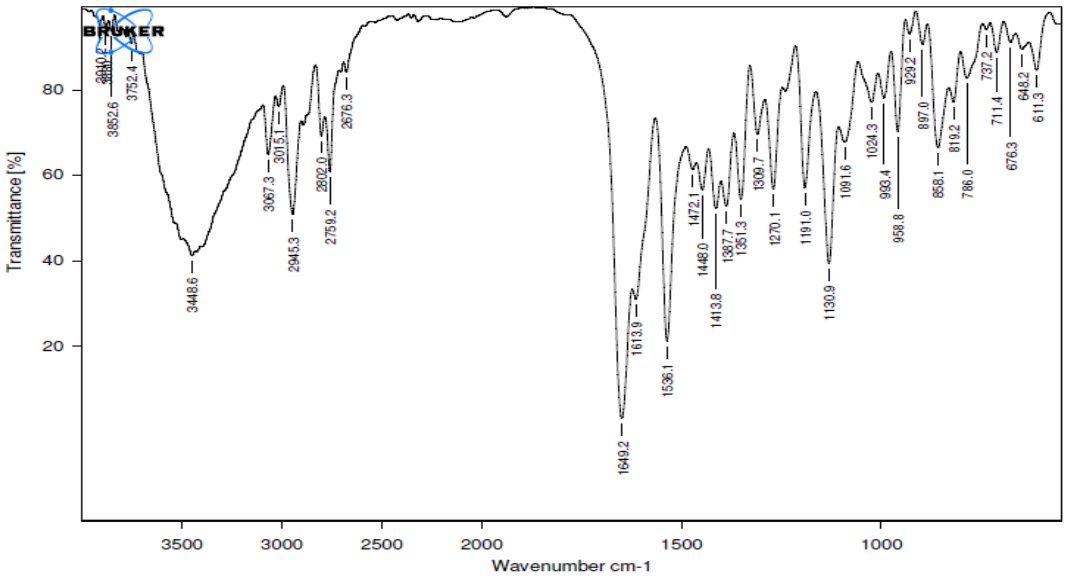

Fig 2: FTIR Spectra for best formulation-F3

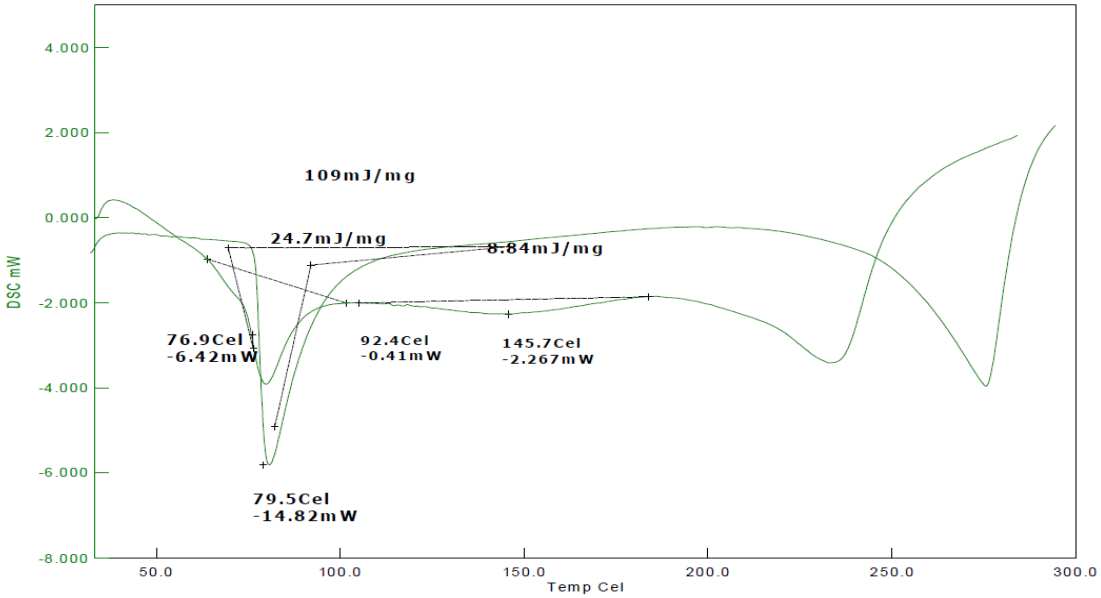

Fig 3: DSC Spectra of empagliflozin

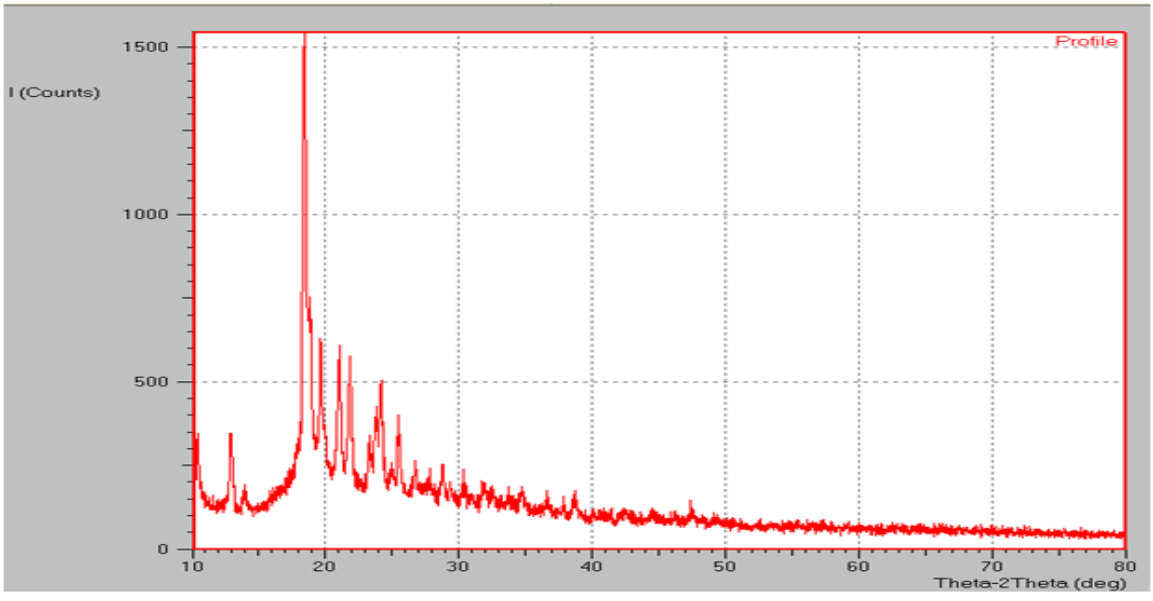

Fig 4: X-Ray diffraction spectra of empagliflozin

Table 2: Pre formulation studies

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausners ratio	Angle of repose (Θ)	Diameter (µm)
F1	0.33±0.01	0.38±0.05	13.33±0.11	1.15±0.02	33.12±0.11	7.01±0.02
F2	0.35±0.03	0.38±0.03	6.98±0.09	1.08±0.06	27.32±0.12	7.08±0.01
F3	0.31±0.01	0.35±0.04	10.42±0.16	1.12±0.08	31.11±0.11	7.03±0.03
F4	0.33±0.05	0.37±0.05	10.87±0.07	1.12±0.07	31.52±0.16	6.92±0.01
F5	0.36±0.02	0.38±0.08	7.14±0.07	1.08±0.03	27.69±0.15	7.11±0.02
F6	0.32±0.06	0.38±0.02	14.89±0.12	1.18±0.05	35.28±0.09	6.89±0.03
F7	0.32±0.09	0.36±0.08	10.64±0.16	1.12±0.09	31.88±0.14	6.95±0.02
F8	0.38±0.05	0.43±0.02	10.26±0.11	1.11±0.03	30.51±0.13	7.02±0.03
F9	0.33±0.04	0.38±0.04	11.11±0.12	1.13±0.07	32.27±0.06	7.04±0.01
F10	0.41±0.03	0.47±0.02	13.51±0.16	1.16±0.06	33.71±0.03	7.19±0.02
F11	0.43±0.06	0.48±0.01	11.43±0.09	1.13±0.04	32.64±0.13	6.85±0.01
F12	0.31±0.03	0.36±0.06	12.50±0.07	1.14±0.01	33.7±0.07	7.13±0.03
F13	0.33±0.05	0.37±0.04	10.87±0.02	1.12±0.07	31.29±0.02	6.91±0.02
F14	0.27±0.01	0.30±0.05	10.71±0.06	1.12±0.02	31.75±0.04	7.03±0.01
F15	0.33±0.04	0.38±0.04	13.33±0.03	1.15±0.05	33.95±0.03	7.09±0.01
F16	0.43±0.03	0.50±0.06	14.29±0.03	1.17±0.07	34.96±0.11	6.92±0.04
F17	0.41±0.01	0.45±0.05	10.81±0.01	1.12±0.04	31.69±0.15	6.89±0.01
F18	0.35±0.02	0.39±0.06	11.63±0.06	1.13±0.03	32.56±0.14	7.05±0.03

Table 3: Post compression studies

Post compression studies					
Formulation code	**Weight variation**	**Thickness**	**Hardness**	**Friability**	**Drug content**
F1	Pass	2.52±0.06	8.23±0.11	0.32±0.01	96.01±0.14
F2	Pass	2.57±0.01	8.10±0.02	0.15±0.05	96.82±0.18
F3	Pass	2.49±0.04	8.31±0.05	0.41±0.03	99.85±0.13
F4	Pass	2.52±0.08	8.17±0.02	0.27±0.04	97.03±0.21
F5	Pass	2.55±0.06	7.96±0.07	0.35±0.02	97.05±0.16
F6	Pass	2.57±0.04	8.21±0.03	0.16±0.04	97.11±0.18
F7	Pass	2.57±0.01	8.06±0.03	0.26±0.06	96.29±0.13
F8	Pass	2.51±0.07	7.94±0.02	0.36±0.04	97.69±0.16
F9	Pass	2.48±0.03	8.16±0.01	0.41±0.03	97.85±0.16
F10	Pass	2.46±0.01	8.32±0.06	0.28±0.06	97.31±0.18
F11	Pass	2.55±0.06	8.16±0.11	0.22±0.04	98.03±0.14
F12	Pass	2.53±0.04	8.17±0.14	0.16±0.07	99.56±0.13
F13	Pass	2.46±0.01	8.25±0.08	0.19±0.04	96.93±0.17
F14	Pass	2.42±0.03	8.17±0.03	0.07±0.05	97.52±0.14
F15	Pass	2.51±0.02	8.35±0.02	0.31±0.03	97.67±0.17
F16	Pass	2.55±0.01	8.35±0.01	0.24±0.02	96.04±0.19
F17	Pass	2.41±0.04	7.86±0.04	0.17±0.01	96.08±0.21
F18	Pass	2.52±0.01	8.19±0.07	0.12±0.03	96.38±0.27

Dissolution Studies

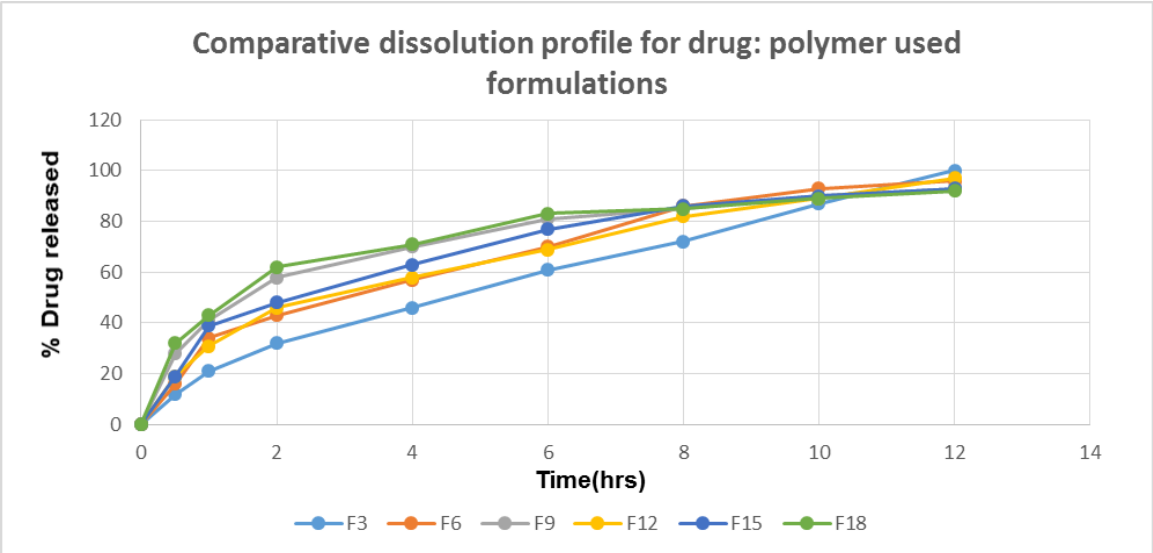

Fig 5: Comparative dissolution studies of Drug: Polymer ratio for different polymers

Conclusion

Present study was aimed to develop and evaluate anti-diabetic sustained release oral tablet of Empagliflozin. On the basis of literature survey and Compatibility Tests, excipients like Microcrystalline Cellulose, Magnesium Stearate were used. In present study, the tablets were prepared by using direct compression technique. In order to optimize the product, different formulations were developed. All the formulations were evaluated for physical characteristics, *in-vitro* dissolution studies. The blends were analysed for the parameters such as Bulk density, Tapped density, Compressibility index, Hausner's ratio, Angle of repose and results were found to be within the limits. Based on the results of dissolution studies and marketed formulation, F3 was found to be the best among trails. It concludes that direct compression of spherical crystallization of Empagliflozin with selective polymers is an efficient method to improve compressibility and also dissolution profile of Empagliflozin.

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