folia medica

Folia Medica 64(3):488-500
DOI: 10.3897/folmed.64.e68866

Original Article

A Recent Solidification Approach for Nanosuspension: Formulation, Optimisation and Evaluation of Canagliflozin Immediate Release Pellets

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Received: 22 May 2021 ♦ **Accepted:** 2 Aug 2021 ♦ **Published:** 30 June 2022

Citation: Patel NC, Patel HA. A recent solidification approach for nanosuspension: formulation, optimisation and evaluation of canagliflozin immediate release pellets. Folia Med (Plovdiv) 2022;64(3):488-500. doi: 10.3897/folmed.64.e68866.

Abstract

Introduction: Canagliflozin is a BCS class IV drug. Nanosuspension is known to enhance the saturation solubility and dissolution rate of poorly soluble drugs owing to the increased surface area of nanosized particles.

Aim: In the present study, we aimed to improve the dissolution characteristics of a poorly water-soluble drug canagliflozin by nanosuspension formulation and stability of this solubility enhancing system - nanosuspension can be improved by converting them into solidified forms as immediate release pellets.

Materials and methods: Canagliflozin nanosuspension was formulated using the media milling method. Poloxamer 407 was used to stabilise nanosuspension. Prepared nanosuspensions were subjected to the characterisation of particle size, polydispersity index (PDI), and drug content. Optimised nanosuspension (NS1) was solidified by converting into immediate release pellets: as improved stability, where canagliflozin nanosuspension was used as a binder. Pellets were prepared by +extrusion-spheronization technique using microcrystalline cellulose (MCC) as pelletizing aid and sodium starch glycolate as super disintegrant. Different important process parameters e.g. concentration of sodium starch glycolate (A), spheronization speed (B) and spheronization time (C) were investigated by 2^3 factorial design to accomplish desired disintegration time (R1) and drug release at 10 min (R2).

Results: The optimised nanosuspension had 120.5 nm particle size, 99.14% drug content and the optimised immediate release pellets (PF5) disintegrated within 23.29 second, and had 99.11% drug content. In vitro dissolution studies showed 89.59% drug release within 10 min in 0.75% w/v SLS. Scanning electron microscopy (SEM) confirmed uniform and spherically shaped pellets. Fourier transform infrared spectrometry (FTIR) and differential scanning calorimetry (DSC) analysis reveal no significant interaction between drug and excipients.

Conclusions: It can be concluded from the findings of this study that the formulation of nanosuspension and its use as a binder in the formulation of immediate release pellets should be investigated further in order to improve the dissolution rate and formulation stability.

Keywords

canagliflozin, extrusion, media milling, nanosized, spheronization

INTRODUCTION

Canagliflozin (CFZ) {(1S)-1, 5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]-methyl]-4-methylphenyl]-D-glucitol hemihydrate} is the first drug approved in this class of SGLT-2 inhibitors (also called gliflozin class of drugs).[1,2] It is administered orally as a tablet in a dose of 100 or 300 mg once daily as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus (T2DM).[3,4] Based on low solubility and low permeability, canagliflozin is classified as a BCS 4 drug.[5] The FDA database of the patented product INVOKANA® mentions that canagliflozin shows dose-dependent adverse effects.[6] The formulation and design of a dosage form require consideration of the physical, chemical and biological characteristics of all the drug substances and pharmaceutical ingredients to be used in its preparation. Solubility is an important property of a drug substance, especially in aqueous medium.[7,8] The formulation of weakly soluble chemicals like canagliflozin into nanometer-sized particles, generally less than 1 μm in diameter, is an attempt to boost dissolution rate and affect saturation solubility. When the drug particle size is reduced from 8 μm to 200 nm, the surface area to volume ratio increases 40-fold, resulting in a significant rise in the dissolution rate if the formulation disperses into discrete particles.[9]

One of the major challenges of the pharmaceutical researchers is to develop an enabling formulation which can make poorly water-soluble drugs highly soluble to overcome the low bioavailability problem of the drugs. Many strategies have been used to improve the aqueous solubility of poorly soluble drugs such as complexation[10], micronisation[11], lipid based formulations, use of cosolvents, solid dispersions[12], pellets[13], etc. However, these techniques often lead to poor solubility, toxicity, high production costs[14] and therefore fails at commercial level.

Nanotechnologies are one of the most prevalent strategies not only for overcoming the problem of poor solubility and thus bioavailability, but also for targeted drug delivery. Nanosuspensions are submicron dispersions of nanosized drug particles stabilised by surfactants, polymers, or a mixture of both.[15] They combine the advantages of nanotherapeutics (the increased dissolution rate and saturation solubility) with ease of commercialisation. Conversion of nanosuspensions to solid oral and other dosage form reduces the physical instability associated with their liquid state, enhances patient compliance, and solid state ensures their long-term stability. Various drying techniques, with some of them well established (e.g. spray drying) while others are less applied in pharmaceutical technology. However, these methods may lead to the increased cost of the product. Thus, an approach is required that would not only provide solubility improvement but also impart stability to the formulation during shelf life and which would involve simple techniques that can be easily employed in commercial production.

Pellets are a multiunit dosage form of fine powders or granules of bulk drugs and excipients. They range in size typically from about 0.5 mm to 1.5 mm of small, free flowing, spherical or semi-spherical solid units and are intended usually for oral administration. Extrusion-spheronization is a versatile method for obtaining pellets of high density, narrow particle size distribution, and high drug loading.[16] Most of the pellet formulations for extrusion/spheronization include microcrystalline cellulose (MCC) as the main excipient, which is the most widely used excipient for the production of pellets due to proper rheological properties, cohesiveness and plasticity to produce spherical particles from its wet masses.[17] However, its applicability is limited particularly in case of poorly water soluble drugs due to its non-disintegration behaviour of the MCC pellets. This, in turn, decreases the release rate of drugs from the pellets. This limitation of MCC pellets has been overcome using a variety of pharmaceutical formulation approaches. They include the use of 40% of isopropanol/water mixture as a granulating binder or incorporation of superdisintegrants into MCC pellets.[18] The present research describes enhancement of dissolution rate of canagliflozin from MCC pellets by incorporating a varied proportion of superdisintegrant (sodium starch glycolate) and water soluble components (poloxamer 407).

In the present study, canagliflozin was used as a model drug and its nanosuspensions were prepared using the media milling method for the dissolution improvement. Optimised nanosuspension was used as a binder for the preparation of immediate release (IR) pellets, where MCC was used as a pelletizing agent and sodium starch glycolate as disintegrant and optimise the formula using the 2^3 factorial design by extrusion-spheronization technique. Physicochemical properties of nanosuspension including particle size and polydispersity index, and % drug content were evaluated. As the disintegration of the pellets leads to an increase in the surface area of the drug which is already in nanosize, stabilizing nanosuspension by converting it to immediate release pellets would improve the solubility, stability, and the dissolution rate of the drug

AIM

This study aims to improve the solubility of a drug by nanosuspension, and the transformation of nanosuspensions to the solid state ensures their long-term stability and increases patient compliance. Canagliflozin was used as a model drug and its nanosuspensions were prepared using the media milling method to improve the dissolution. An optimised nanosuspension was used as a binder for the preparation of immediate release (IR) pellets, where the MCC was used as a pelletizing agent and sodium starch glycolate (SSG) by extrusion-spheronization technique. The prepared pellets were optimised and evaluated for different characteristics and improved the dissolution compared to the pure drug and marketed product.

MATERIALS AND METHODS

Materials

Canagliflozin (gift sample from Zydus Cadila Pvt. Ltd, Ahmedabad). Poloxamer 407 (BASF Corporation, USA.) Zirconium oxide beads (0.5 mm) (gift sample from Synco Industries Limited, India.) Microcrystalline cellulose, corn starch, sodium starch glycolate and Kyron T 314 (gifts sample from Shiva Health Care, Mehsana). All chemicals we used were analytical and pharmaceutical grade. Distilled water was used throughout the study.

Methods

Preparation of canagliflozin nanosuspension

Nanosuspension of canagliflozin was prepared using wet media milling method.[19] Suspensions of 100 mg canagliflozin in 10 ml distilled water were prepared in 20 ml vials using zirconium oxide beads (0.5 mm) as a milling medium with different concentration of poloxamer 407 stabiliser. As per a previous study for nanosuspension of canagliflozin was indicated among all the stabiliser, poloxamer 407 showing the lowest mean particle size and the highest drug release in 10 min. It also showed a minimum PDI showing uniformity in particle size of nanosuspension and indicating greater stability. Therefore, poloxamer 407 was selected as a stabiliser for further studies. The drug was directly added into the stabiliser solution. These were comminuted with different amounts of zirconium oxide beads on a magnetic stirrer for 16 and 24 hrs. Nanosuspension was separated from the Zirconium Oxide beads by decanting the suspension followed by washing the beads with water. The processing temperature was maintained at 32°C. Based on trial batches of canagliflozin nanosuspension in my previous research work[19], different batches were prepared by varying the levels of both formulation and process variables such as amount of stabiliser in mg, stirring time in hours, amount of zirconium oxide beads in gm, and stirring speed in rpm. Compositions of different batches of canagliflozin nanosuspensions are shown in **Table 1**. The resulting nanosuspensions were evaluated and the optimised nanosuspension was converted in pellets.

Characterisation of canagliflozin nanosuspension

Particle size distribution and polydispersity index (PDI)

Particle size was determined by photon correlation spectroscopy using a Zetasizer 3000 (*z*-average, measuring range 20–1000 nm, Malvern Instruments, UK). All presented data are the means of the values for three independent samples obtained under identical conditions. Once the required intensity was reached, analysis was performed to get the mean particle size and polydispersity index(PDI).[19]

Drug content

An aliquot (1 ml) of the nanosuspension was diluted in methanol and diluted with 0.75% w/v of SLS, then filtered with a 0.2-µm filter. The total drug content was determined by UV spectrophotometer at λ_{max} of the drug.[20]

Formula:

$$\text{Total Drug Content} = \frac{(\text{Total volume of nanosuspension} \times \text{Amount of drug in aliquot})}{\text{Volume of aliquot}}$$

Preparation of immediate release pellets

Pellets were prepared using the extrusion-spheronization technique.[17] Initially eight placebo batches were prepared in order to optimise the formula on the basis of evaluation parameters **(Table 2)**. The excipients were weighed and mixed intimately in a mortar for 15 min. Distilled water as binder was added to the mixture and wet mass was prepared. The wet mass was extruded using single screw extruder (Umang Pharmatech Pvt. Ltd, Mumbai, India) and spheronized for ten minutes at varying speed in a spheronizer (Umang Pharmatech Pvt. Ltd, Mumbai, India) fitted with cross-hatched rotor plate with a diameter of 150 mm and thickness 3 mm. The resulting pellets were dried to constant weigh at 40°C and were subjected to further evaluation. Preliminary screening for selection of pelletizing aid, super disintegrants, other excipients and instrument parameters was done by visual inspection and flow properties of the pellets obtained from the initial studies. Microcrystalline cellulose and corn starch were used as pelletizing aids[20] whereas sodium starch glycolate (SSG)

Table 1. Composition of formulation of batches of canagliflozin nanosuspension

Formulation code	Amount of drug mg	Amount of stabiliser mg	Amount of ZrO_2 beads mg	Stirring time hour	Stirring speed rpm
NS1	100	100	8	16	1000
NS2	100	100	8	16	600
NS3	100	50	8	24	600
NS4	100	50	4	24	1000
NS5	100	50	4	16	600

Table 2. Composition of placebo batches of IR pellets

Formulation code	MCC % w/w	Corn starch % w/w	SSG % w/w	Kyron- 314 % w/w	Lactose % w/w
P1	30		10	---	60
P2	30		---	10	60
P3	20		15	---	65
P4	20		---	15	65
P5	20		10	10	60
P6	---	30	---	10	60
P7	---	20	10	10	60
P8	---	30	10	---	60

and Kyron T 314 were used as super disintegrants. After optimisation of the formula, the immediate release pellets of canagliflozin were prepared by applying 2^3 factorial design using nanosuspension as a binder.[13]

From the formulation and production result, it was observed that microcrystalline cellulose was used as pelletizing aids and sodium starch glycolate as super disintegrant, gave acceptable spherical pellets with good yield, low friability and satisfactory flow properties. Based on the observations, 30% of MCC, 10% of SSG and spheronization speed of 800 rpm with time 10 mm were selected as formulation and process parameters.

Formulation and optimisation of canagliflozin pellets by using 2^3 factorial design

In order to study the effect of processing and formulation variable on canagliflozin pellets, 2^3 factorial design was utilised by using Design Expert 12.0. This design consisted of 8 experimental trials **(Table 3)**, with 2 levels of 3 independent variables. The independent variables include conc. of sodium starch glycolate (A) at 5 and 10%, spheronization speed (B) at levels 600, 900 rpm, and spheronization time (C) at 10, 15 min selected for evaluation of immediate release pellets were as disintegration time (R1) and drug release at 10 min (R2) and as dependent variables.

$$R = \beta_0+\beta_1 A+\beta_2 B+\beta_3 C$$

Characterisation of drug loaded pellets

Determination of micromeritic properties[22]

Tap density and bulk density of the pellets were determined by tap density tester (Electro lab).

The angle of repose (θ) was measured by a fixed funnel method to know the flowability of the pellets.

$$\text{Tan}(\theta) = h/r$$

where 'h' and 'r' are respectively the height and radius of the powder cone.

The Carr's compressibility index (%) of the pellets was determined using following formula:

Carr's Compressibility Index (%) =
(Tapped density- Bulk density)/Tapped density

Hausner's ratio of pellets was determined by ratio of tapped density to bulk density.

Friability is the measure of pellet strength. The friability of pellets was determined by using tablet friability tester (Electro lab) for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion and to generate friability index. The pellets were then dedusted and reweighed.

$$\text{Friability (\%)} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

Table 3. Composition of factorial batches

Formulation code	A: Conc. of SSG %	B: Spheronization speed rpm	C: Spheronization time min	MCC % w/w	Lactose % w/w	Drug mg
PF1	5	900	15	30	55	100
PF2	5	600	15	30	55	100
PF3	5	900	10	30	55	100
PF4	5	600	10	30	55	100
PF5	10	600	10	30	60	100
PF6	10	600	15	30	60	100
PF7	10	900	10	30	60	100
PF8	10	900	15	30	60	100

Particle size and size distribution[21]

The size and size distribution of the pellets produced was determined by agitation for 10 min with a sieve shaker (Rotap LHC-41) fitted with a progression of standard sieves. From the weight retained on each sieve, particle size is determined from standard sieve aperture size as per Indian Pharmacopeia.

Disintegration time[22]

Disintegration time of pellets was determine as 100 mg pellets from each batch in distilled water by tablet disintegration tester (Electro lab) without disc at 37±0.5°C temperature with 30 dips speed. Disintegration test was carried out three times for the Immediate Release formulations and the results were expressed as mean ± standard deviation.

Drug content[22]

Accurately weighed 100 mg pellets were taken and converted in fine using mortar and pestle and the powder was dissolved in methanol using sonication and diluted with 0.75% w/v of SLS. The UV absorbance of the suitably diluted filtrate was measured at λ_{max} 290 nm to determine the drug content. The concentration of drug was calculated using a calibration curve.

In vitro dissolution studies[13,19]

In vitro drug release studies of pellets were performed using the USP Apparatus I (basket) at a speed of 75 rpm in 900 ml of 0.75% w/v of SLS and the medium at 37.0±2°C. Canagliflozin is soluble in many organic solvents (methanol, dimethyl sulfoxide) and insoluble in aqueous media and freely soluble in 0.75% w/v of SLS.[23,24] We selected 0.75% w/v of SLS as dissolution medium. Pellets equivalent to 100 mg of the drug were weighed and added in to it. At predetermined time intervals, 10 ml of sample was withdrawn and the dissolution medium was kept constant by refilling it with fresh buffer solution to maintain sink conditions. The collected samples were filtered, suitably diluted, and analysed at 290 nm using UV-Visible spectrophotometer. Dissolution rate profiles of IR pellets were compared with the marketed tablet formulation of canagliflozin (Invokana 100 mg) and pure drug in order to investigate the potential of immediate release pellets in improving the dissolution rate.[20,21]

X-ray diffraction[23]

X-ray diffractometer (Xpert MPD Philips, Holand) was used for qualitative powder x-ray diffraction of pure canagliflozin, physical mixture of excipients and final pellets (PF5). The instrument was operated at a voltage of 40 KV and a current of 30 mA, with copper as the tube anode material. The samples were run over a range of 2θ angles from 2° to 40°.

Fourier transform spectroscopy analysis[24]

The infrared spectra of the samples were obtained using a compact Fourier transform infrared spectrometry (FT-IR) spectrometer ALPHA II (BRUKER, Germany). 1-2 mg of fine solid powder of sample was directly analysed over the region 400 to 4000 cm^{-1} in the instrument.

Differential scanning calorimetry[24]

The DSC thermogram was obtained by differential scanning calorimeter (DSC), on Shimadzu TA-60 model. The samples were hermetically sealed in an aluminum crucible before analysis. The system was purged with nitrogen gas at a flow rate of 40-50 ml/min. Heating was done between 50°C to 300°C at the rate of 10°C/min.

Scanning electron microscopy (SEM)[25]

The surface morphology and cross section of the optimised pellets was examined by scanning electron microscopy (Nova Nano SEM 450 FEI). The samples were scanned at a voltage of 20 kV with different magnification.

RESULTS AND DISCUSSION

Characterisation and optimisation of canagliflozin nanosuspension

Canagliflozin nanosuspensions were prepared using wet media milling method. The prepared nanosuspensions were clear and transparent due to reduced particle size. The effect of amount of stabiliser, amount of ZrO_2 beads, spheronization time, and spheronization speed were studied on the attributes of nanosuspension. Particle size distribution is a very important parameter because reduced particle size helps in the improvement of solubility of pure drug, thereby increasing its dissolution rate **(Table 4)**.

The mean particle size of different batches of canagliflozin nanosuspension was found to be in the range of 120 nm to 300 nm. An optimised batch (NS1) of nanosuspension showed mean particle size of 120.5 nm **(Fig. 1A)** at a ratio of 1:1 (drug:surfactant) and 8 gm ZrO_2 beads with a stirring time of 16 hr at 1000 rpm. In general, the decrease in particle size is observed due to increased stirring speed and amount of ZrO_2 beads, also an optimum concentration of suitable stabiliser to prevent agglomeration. A stabiliser is usually incorporated in a nanosuspension formulation to prevent or slow down the crystal growth of nanoparticles via Ostwald ripening. Nanosuspensions prepared in this study were stabilised by using poloxamer 407. It was seen that when poloxamer 407 was employed, it increased the wettability of canagliflozin particle and hence showed better particle size reduction. This would result in better dispersion of the drug particles and a greater extent of particle size reduction.

The polydispersity index which is 0.217 in case of NS1 and for other formulation in the range of 0.131 to 0.307. This can be attributed to the good wetting property and dispersibility exhibited by the surfactant used in the above ratio. Therefore, the above concentration of the stabiliser was optimised. Impact of further higher ratios of surfactant

Table 4. Evaluation of prepared nanosuspension

Formulation code	Mean particle size (nm) *	Drug content (%)*	Polydispersity index (PDI) *
NS1	120.5±**5.6**	99.14±**0.11**	0.217±**0.23**
NS2	242.6±**7.4**	92.57±**0.25**	0.254±**0.58**
NS3	246.3±**632**	91.27±0.38	0.281±**1.36**
NS4	179.6±**4.4**	95.42±0.21	0.131±**0.84**
NS5	300±**7.8**	91.35±0.15	0.307±**0.29**

* Indicates average of three determinations (mean ± standard deviation, n=3)

on the particle size reduction and stability was not explored and can be further investigated. It seems reasonable to postulate that use of optimum concentration of suitable stabiliser and stirring rate results in fine nanosuspension with smaller and more uniform particle size.

Zeta potential of optimised canagliflozin loaded nanosuspension batch NS1 was found to be -23.0±4.75 mV which is sufficient for stability **(Fig. 1B)**.

The drug content was determined by UV-visible spectrophotometer method. Formulation NS1 was found to contain the highest drug content amongst the other formulations which is 99.14%.

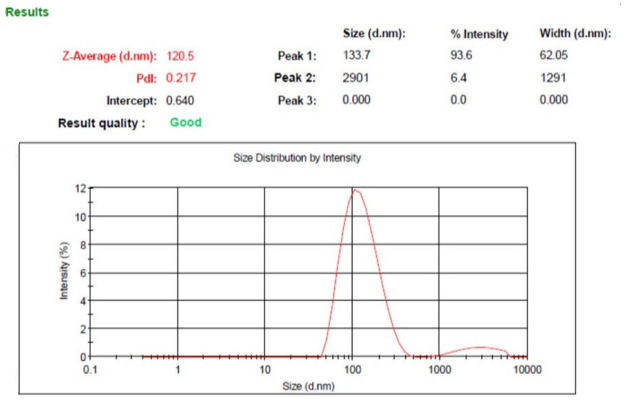

Figure 1A. Particle size distribution of optimum batch NS1.

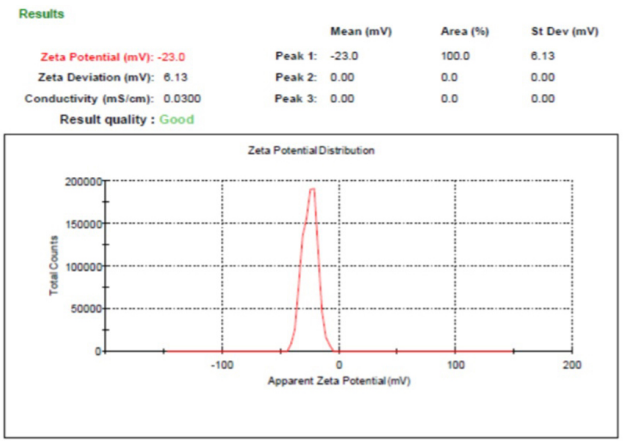

Figure 1B. Zeta potential of optimum batch NS1.

Evaluation of immediate release pellets

Results for the investigation of flow properties indicates good and excellent pellet properties for all the placebo batches. Addition of MCC as a pelletizing agent and sodium starch glycolate as disintegrant results in the improvement of flow. Results for flow properties and drug content of the prepared immediate release pellets factorial batches are presented in **Table 5**.

Density and flow properties

Pellets prepared with MCC and SSG with all batches offered very good physical characteristics and flow properties. Density values for pellets shows that pellets prepared using formula as per batch PF5 produced dense pellets. Pellets prepared from all batch PF1 to PF8 have bulk density and tapped density in the range of 0.59 to 0.79. Due to the spherical shape, the pellets showed smaller angle of repose in the range of 24.28 to 30.54, which is indicative of excellent flowability. The pellets have also very good compressibility.

Friability

Friability is an essential parameter for any drug formulations especially for a potent drug. Pellets prepared within Batch PF5 demonstrated less friability compared to other batches. Pellets produced with different batches have higher friability in the range of 0.41–0.58 which is less than 1. Indicated low product loss because of material during spheronization process due to proper drying of pellets and high speed rotational movement that lead to few dust formation.

Drug content

From the results shown in **Table 5**, it can be concluded that pellets prepared from PF1 to PF8 showed high drug content about 90%. PF5 have a drug content of about 99.11%.

Particle size

The particle size of pellets was determined by sieve analysis. Set of standard sieves were arranged with progression of their sieve number. Based on fraction retained on each

Table 5. Flow properties and drug content of the prepared immediate release pellets factorial batches

Formulation code	Mean particle size μm	Angle of repose	Bulk density gm/ml	Tapped density gm/ml	Hausner's ratio	Carr's index	Friability %	Drug content %
PF1	900	29.24	0.76	0.79	1.03	3.79	0.58	91.24
PF2	850	28.35	0.62	0.64	1.03	3.12	0.55	94.17
PF3	1000	30.54	0.75	0.78	1.04	3.84	0.60	90.31
PF4	700	27.63	0.61	0.65	1.06	6.55	0.51	95.36
PF5	600	24.28	0.59	0.61	1.03	3.38	0.41	99.11
PF6	800	27.21	0.60	0.65	1.08	8.33	0.48	96.84
PF7	750	25.34	0.62	0.66	1.06	6.06	0.58	95.21
PF8	850	25.87	0.64	0.69	1.07	7.25	0.57	94.75

sieve average particle size was calculated that is described in **Table 5**. From the results it can be observed that the particle size of pellets was in the range of 600-1000 μm. It can also be concluded that the pellet size increased with increasing the concentration of SSG which leads to a decrease of the disintegration time and increase of the drug release.

Disintegration time

Disintegration study revealed that the use of different concentration of disintegrants affects the process of disintegration. MCC used alone as pelletizing agent showed a slow disintegration process with a higher disintegrating time, also as the concentration of MCC reduced, the disintegration time also decreased. Addition of disintegrate further lowered the disintegration time **(Table 6)**. With sodium starch glycolate, disintegration time was the lowest (23.29 second, batch PF5), indicating a very rapid disintegration of the pellets. The order of disintegration for different batches was PF1>PF8>PF3>PF2>PF4>PF7>PF6>PF5. Disintegration studies become important for immediate release pellets, where faster drug release is required in gastrointestinal fluids. Faster disintegration will result into greater number of smaller particles in the dissolution medium. This will result in a great increase in surface area and increased water solubility. The rapid disintegration of pellet formulation PF5 can be accounted for by the swelling of MCC and sodium starch glycolate in the presence of disintegration medium.

Results of drug release for batches PF1 to PF8 are shown in **Fig. 2**. All these batches were prepared to study the effect of concentration of different spheronization seed and spheronization time. Drug release of batch PF5 containing 10% and spheronized at 600 rpm for 10 min was found to be higher compared to that of other batches (PF6, PF7, PF8) containing 10%. From the above findings it can be concluded that drug release from pellets increased with the increase in concentration and also with the decrease in spheronization seed and spheronization time. Batch PF5 shows drug release about 89.31% in 10 min. So factorial batch PF5 was selected as optimised for preparing IR pellets containing pure drug and using nanosuspension as a binder.

Data analysis

The polynomial equations for full model relating to the response, disintegration time and drug release at 10 min, the

Table 6. Effect of response variable immediate release pellets DOE batches

Formulation code	A: Conc. of SSG %	B: spheronization speed rpm	C: spheronization time min	R1 disintegration time second *	R2 % drug release at 10 min % *
PF1	5	900	15	36.48±0.5	78.19±1.2
PF2	5	600	15	30.54±0.24	80.28±0.2
PF3	5	900	10	31.27±0.4	79.48±0.35
PF4	5	600	10	28.52±0.87	84.26±0.58
PF5	10	600	10	23.29±1.24	89.31±0.57
PF6	10	600	15	25.34±0.68	84.23±1.34
PF7	10	900	10	26.36±045	86.32±0.89
PF8	10	900	15	32.46±0.24	80.68±0.54

* Indicates average of three determinations (mean ± standard deviation, n=3)

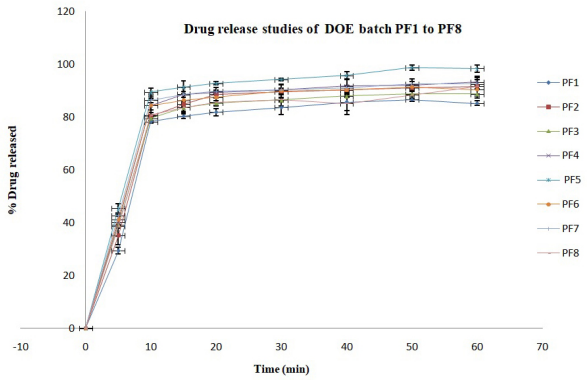

Figure 2. Drug release studies of factorial batches PF1 to PF8.

transformed factor are shown in **Table 7**. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive).

Table 7 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Since the values of R2 are quite high, i.e. 0.9451, the polynomial equations best fit the experimental data and are statistically valid. Coefficients with one factor represent the effect of that particular factor on responses while the coefficients with more than one factor and those with second order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. Positive sign in front of the terms indicates synergistic effect while negative sign indicates antagonistic effect upon the response. So from the above data, it can be observed that concentration of SSG (A) has antagonistic effect whereas spheronization speed (B) and spheronization time (C) have positive coefficient value that indicates synergistic effect on response R1 and reverse for R2. From the equation of the model as shown, it can be qualitatively concluded that A had the largest effect on the response R1 and R2, which indicated that A was a more important parameter to regulate disintegration time and drug release at 10 min.

The contour and surface 3D plots **(Fig. 3)** show the effect of concentration (A), spheronization speed (B) and spheronization time (C) on disintegration time (R1) and drug release at 10 min (R2). As the value of A increases, the value of response R1 decreases and response R2 increases, whereas when B and C increase, the value of response R1 increases and R2 decreases.

It was observed that pellets prepared using nanosuspension (PF5) released more than 89% drug within 10 min as compared to the marketed tablet and pure drug which released only 24.63% and 18.65% drug, respectively within 10 min **(Fig. 4)**. Dissolution of the drug depends on its release from the dosage form, which in turn depends on the disintegration of oral formulation. Drugs with poor solubility face the issue of poor dissolution and absorption after release from the dosage form. This accounts for the poor bioavailability of the drug. Faster disintegration and increase in surface area at the site of dissolution can lead to better and enhanced contact of drug molecules with the physiological fluid and can give a faster rate of dissolution. This combined approach can be achieved by preparing immediate release multiparticulate dosage form of the drug. The immediate release pellets of the drug were prepared with the objective of enhanced dissolution. Significant increase was found in drug release from immediate release pellets as compared to pure drug and marketed formulation.

Solidification approach of nanosuspension by using it as a binder in immediate release pellets resulted in a marked increase in the drug release pattern, which can be due to the synergistic effect produced by the reduced particle size at nano level and delivery of the poorly soluble drug in the form of immediate release pellets. Therefore, it can be concluded that both approaches, i.e. use of nanosuspension as a binder and use MCC for immediate release pellets improved the dissolution rate of canagliflozin.

Table 7. Statistical data from ANOVA test for 2^3 factorial design

Regression statistics				
	R1 Disintegration time second		**R2 Drug release at 10 min %**	
R^2	0.9451		0.9450	
Adjusted R^2	0.9039		0.9037	
Predicted R^2	0.7803		0.7800	
Mean standard error	0.4688		0.4188	
Observation	8		8	
	Coefficient	***P* value**	**Coefficient**	***P* value**
Intercept	29.28	0.0056	82.84	0.0056
A-conc. of SSG	-2.42	0.0067	2.29	0.0054
B-spheronization speed	2.36	0.0073	-1.68	0.0161
C-spheronization time	1.92	0.0148	-2.00	0.0088
Equation: full model	DISINTEGRATION TIME = +29.28-2.42A+2.36B+1.92C		DRUG RELEASE AT 10 MIN = +82.84+2.29A-1.68B-2.00C	

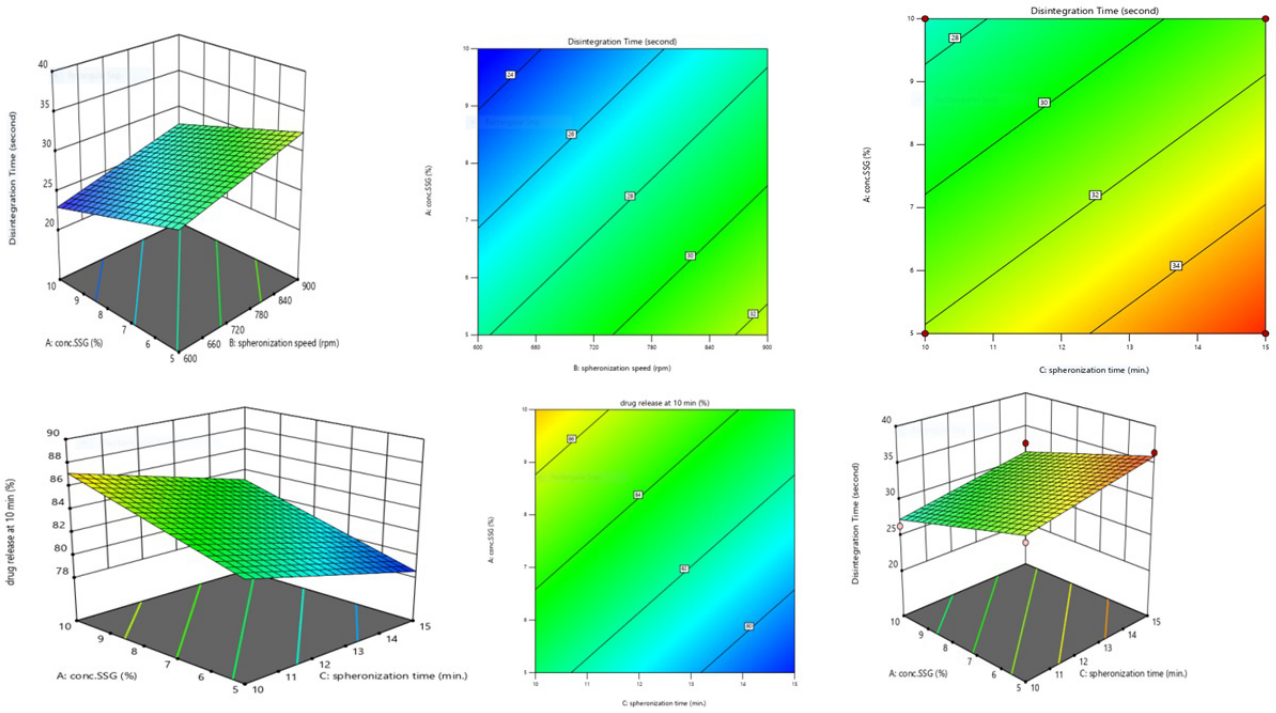

Figure 3. Contour plot and surface 3D plot of dependent and response variables.

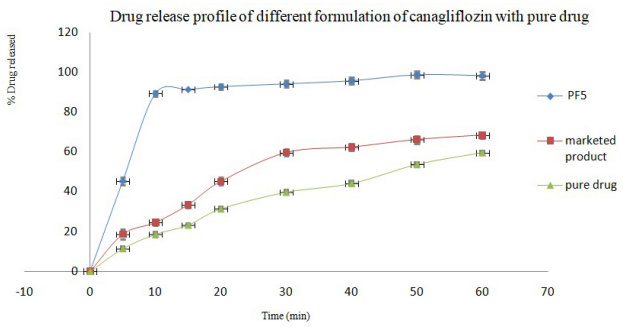

Figure 4. Drug release profile of different formulation of canagliflozin with pure drug.

X-ray diffraction

X-ray diffraction was used to analyse the potential changes in the inner structure of canagliflozin during the formulation. X-ray diffractogram of pure canagliflozin, physical mixture of excipients and final pellets (PF5) exhibited several peaks at different intensities between 2° to 40° **(Fig. 5)**. While the X-ray diffractogram of optimised formulation show less intense peak as in drug. From the obtained peaks, it revealed that the crystalline nature of drug is not affected significantly in the final formulation.

Fourier transform spectroscopy analysis

The FTIR spectra of canagliflozin pellets (PF5) and nanosuspension (NS1) when compared with IR spectra of canagliflozin pure drug, showed no interaction of drug with excipient, indicating the compatibility of the drug with the excipient. Hence principle peaks of canagliflozin can be seen in the IR spectra of both formulation **(Fig. 6)**. There was no shifting of peaks found. From the spectra, it can be concluded that canagliflozin remains unaffected during the process of extrusion and spheronization in the presence of MCC and SSG.

Differential scanning calorimetry (DSC)

The DSC thermogram of pure drug, physical mixture of all excipient and pellet batch (PB5) is shown in **Fig. 7**. The thermogram of canagliflozin show a peak at 108.10°C whereas in the thermogram of physical mixture of all excipients and pellet batch (PB5), the peaks are at 109.37°C and 106.31°C, respectively, hence there is no change in the drug peak. It was found that all the excipients used in the formulation do not affect the melting point of the drug. This confirmed that there was no incompatibility between drug and excipients.

Scanning electron microscopy

The morphology of optimised pellets PF5 analysed by scanning electron microscopy is shown in **Fig. 8**. The uniform round spherical pellet and size of pellet diameter was found to be 513.4 µm. The surface texture of the prepared pellets was smooth and had few pores that will be responsible for rapid disintegrating property of pellets.

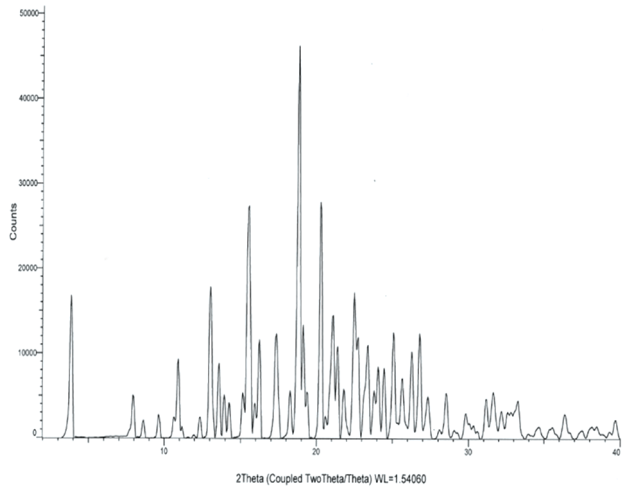

Figure 5A. X-ray diffractogram pure of canagliflozin.

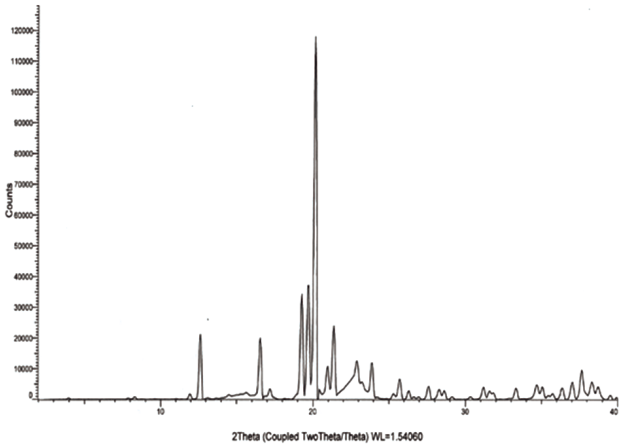

Figure 5B. X-ray diffractogram of physical mixture of excipients.

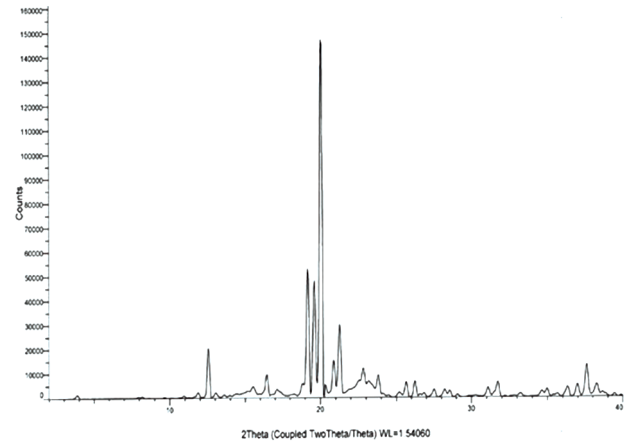

Figure 5C. X-ray diffractogram of canagliflozin pellets (PF5).

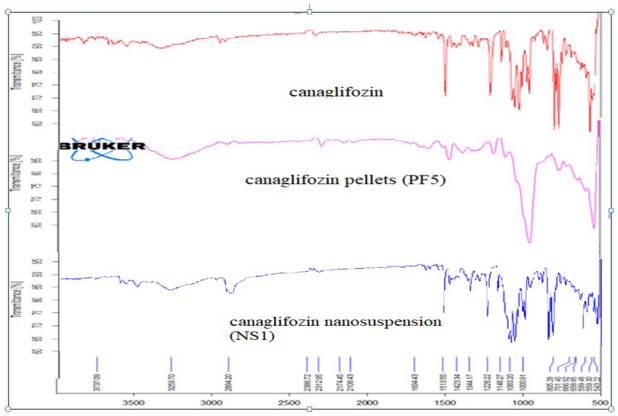

Figure 6. FTIR spectra of canagliflozin, canagliflozin pellets (PF5), canagliflozin nanosuspension (NS1).

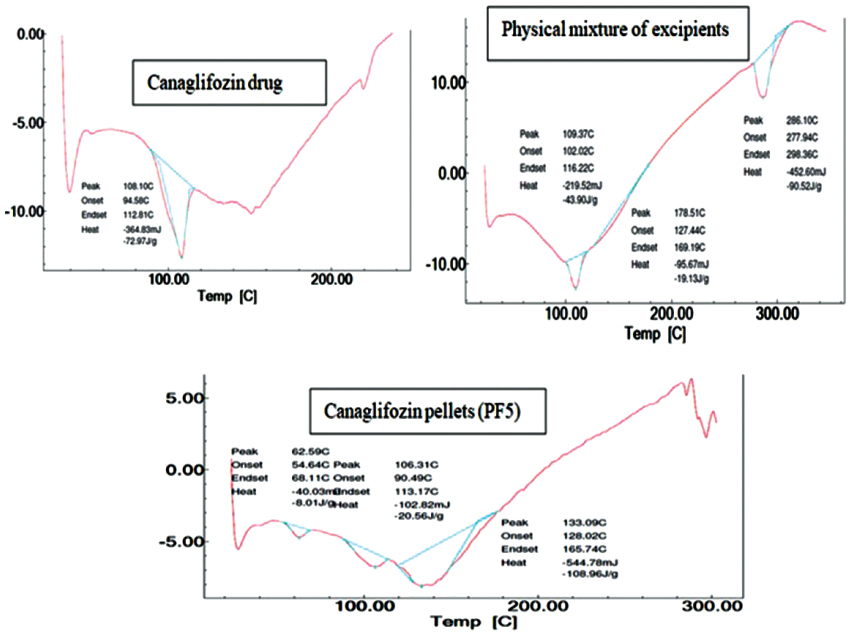

Figure 7. DSC thermogram of canagliflozin, physical mixture of excipients, canagliflozin pellets (PF5).

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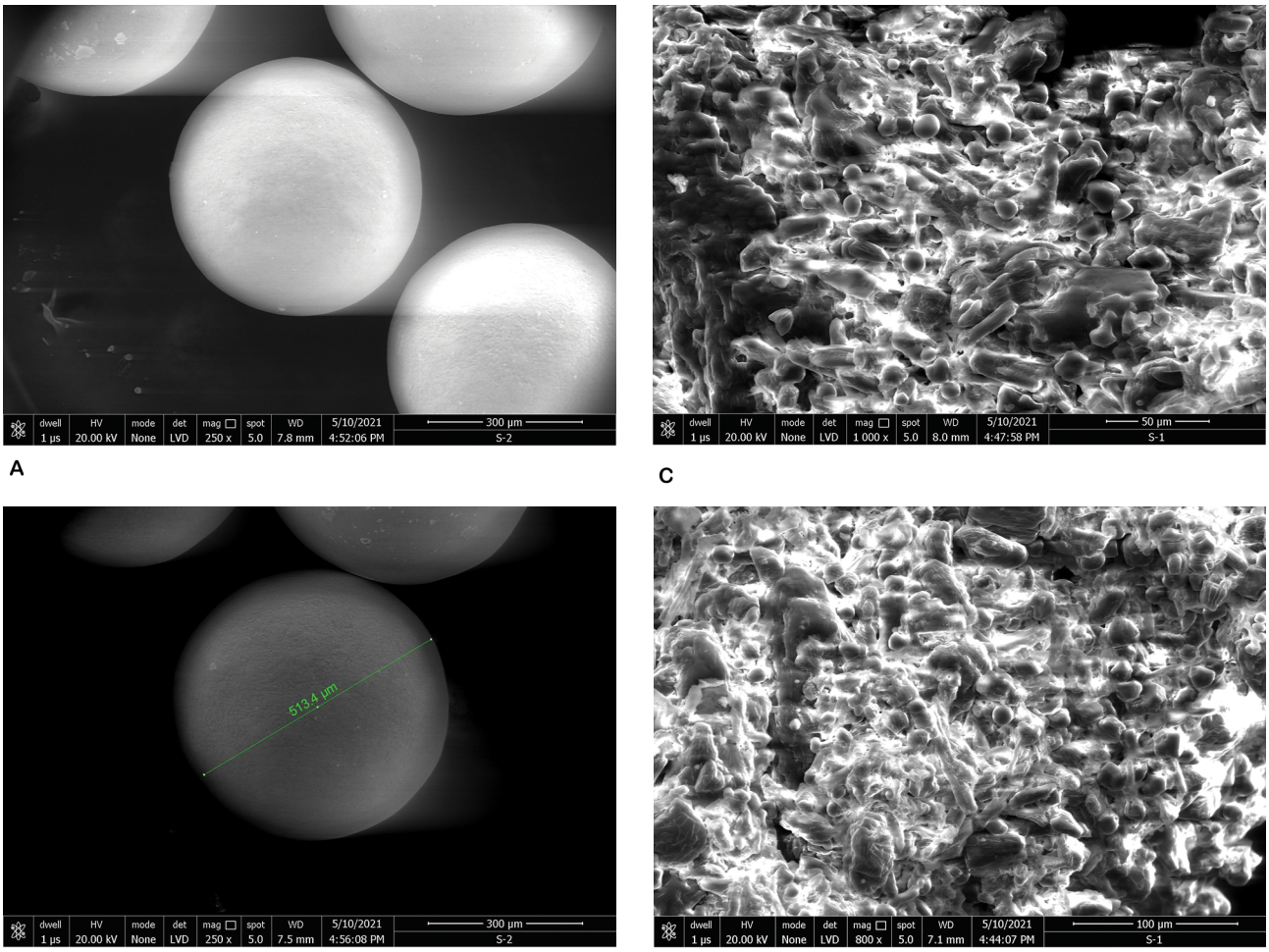

Figure 8. SEM images of pellets and pellet surface.

CONCLUSIONS

On the basis of the results of the present study, we can conclude that the formulation of immediate release pellets using nanosuspension as a binder can be a unique and feasible option for stabilisation as well as solidification of nanosuspensions. Use of wet media milling method as a non-specific technique for size reduction can produce nanosuspension with significant improvement in dissolution rate. The study has demonstrated that it is possible to enhance the solubility of canagliflozin by preparing its nanosuspension using a media milling technique. Furthermore, the solubility of the drug can be improved by formulating immediate release pellets using MCC and SSG to improve the dissolution rate. Solidification of nanosuspension as pellets can be further explored for increasing the solubility of other poorly soluble drugs and stabilisation of nanosuspension.

Acknowledgements

The authors express their gratitude to Zydus Cadila Pvt. Ltd., Synco Industries Limited and Shiva Health Care for providing gift samples. The authors are thankful to the management of SSKM, Gujarat for providing the facilities to carry out the research work and Sophisticated Instrumentation Centre for Applied Research & Testing (SICART) for providing facility of XRD and SEM.

Conflict of Interest

The authors declare no potential conflict of interest. The authors alone are responsible for the design of the study, the content and writing of the manuscript.

Author contributions

All authors have equal contribution to project work, data analysis and writing paper.

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Новый подход к отверждению наносуспензий: рецептура, оптимизация и оценка гранул с немедленным высвобождением канаглифлозина

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Дата получения: 22 мая 2021 ♦ **Дата приемки:** 2 августа 2021 ♦ **Дата публикации:** 30 июня 2022

Образец цитирования: Patel NC, Patel HA. A recent solidification approach for nanosuspension: formulation, optimisation and evaluation of canagliflozin immediate release pellets. Folia Med (Plovdiv) 2022;64(3):488-500. doi: 10.3897/folmed.64.e68866.

Резюме

Введение: Канаглифлозин является препаратом IV класса согласно Биофармацевтической системы классификаций BCS. Известно, что наносуспензия повышает растворимость при насыщении и скорость растворения малорастворимых лекарственных средств за счёт увеличения площади поверхности наноразмерных частиц.

Цель: В настоящем исследовании мы стремились улучшить характеристики растворения плохо растворимого в воде лекарственного средства канаглифлозина с помощью состава наносуспензии и стабильности этой системы, повышающей растворимость – наносуспензия может быть улучшена путём преобразования их в отверждённые формы в виде гранул с немедленным высвобождением.

Материалы и методы: Наносуспензию канаглифлозина готовили методом измельчения в среде. Для стабилизации наносуспензии использовали полоксамер 407. Приготовленные наносуспензии подвергали характеристике размера частиц, индекса полидисперсности (PDI) и содержания лекарственного средства. Оптимизированная наносуспензия (NS1) была отверждена путём преобразования в гранулы с немедленным высвобождением: в качестве улучшенной стабильности, где в качестве связующего использовалась наносуспензия канаглифлозина. Гранулы готовили методом экструзии-сферонизации с использованием микрокристаллической целлюлозы (МКЦ) в качестве вспомогательного средства для гранулирования и крахмалгликолята натрия в качестве суперразрыхлителя. Различные важные параметры процесса, например. концентрацию крахмалгликолята натрия (A), скорость сферонизации (B) и время сферонизации (C) исследовали с помощью 2^3-факторного дизайна для достижения желаемого времени дезинтеграции (R1) и высвобождения лекарственного средства через 10 минут (R2).

Результаты: Оптимизированная наносуспензия имела размер частиц 120.5 nm, содержание лекарственного средства 99.14%, а оптимизированные гранулы с немедленным высвобождением (PF5) распадались в течение 23.29 секунды и содержали лекарство 99.11%. Исследования растворения *in vitro* показали высвобождение 89.59% препарата в течение 10 минут в 0.75% w/v SLS. Сканирующая электронная микроскопия (СЭМ) подтвердила однородность гранул сферической формы. Инфракрасная спектрометрия с преобразованием Фурье (FTIR) и анализ дифференциальной сканирующей калориметрии (DSC) не выявили значительного взаимодействия между лекарственным средством и вспомогательными веществами.

Заключение: Из результатов этого исследования можно сделать вывод, что состав наносуспензии и её использование в качестве связующего в составе пеллет с немедленным высвобождением следует дополнительно изучить, чтобы улучшить скорость растворения и стабильность состава.

Ключевые слова

каналифлозин, экструзия, измельчение сред, наноразмеры, сферонизация