IJPSR (2020), Volume 11, Issue 5 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 21 June 2019; received in revised form, 06 March 2020; accepted, 26 March 2020; published 01 May 2020

SPHERICAL CRYSTALLIZATION OF SITAGLIPTIN PHOSPHATE MONOHYDRATE FOR FORMULATION OF DIRECTLY COMPRESSIBLE TABLETS

M. C. Singh * and R. R. Loharkar

Smt. Kashibai Navale College of Pharmacy, S. No. 40/4 A, Near PMC Octroi Post, Kondhwa Saswad Road, Kondhwa, Pune - 411048, Maharashtra, India.

Keywords:

Sitagliptin phosphate monohydrate, Spherical crystallization, Direct compression, 3^2 factorial design, Bioavailability, Solubility

Correspondence to Author:
Dr. (Mrs.) M. C. Singh

Associate Professor
Smt. Kashibai Navale College of Pharmacy, S. No. 40/4 A, Near PMC Octroi Post, Kondhwa Saswad Road, Kondhwa, Pune - 411048, Maharashtra, India.

E-mail: meera.singh@sinhgad.edu

ABSTRACT: Sitagliptin was invented in 2006 as a DPP-4 inhibitor. It is soluble in water to the extent of 0.03 mg/mL as thus suffers bioavailability problems. It was converted into phosphate monohydrate salt with solubility 50 mg/mL, which solved bioavailability problems. In this research, an attempt is made to convert it from its crystalline form into spherical crystals. Spherical crystals have better bulk properties and can adapt to direct compression tableting. This kind of innovation saves the time needed for granulation and can be compressed directly just by adding lubricant and disintegrant. In this research sitagliptin, phosphate monohydrate was made as spherical crystals using water as a solvent, ethanol as anti-solvent, and chloroform as bridging liquid. 3^2 factorial designs for optimization was applied to get an optimized batch with a concentration of bridging liquid and anti-solvent as independent and Carr's index and yield as dependent variables. Batch F7 was considered optimized with a yield of 97.5%. Spherical crystals thus obtained were characterized using X-Ray diffraction, SEM, % compressibility, and flowability. The spherical crystals were directly compressible after adding 8% SSG and 2% magnesium stearate. The resultant tablets were film-coated using HPMC 2910. It was compared with a marketed film-coated tablet, both having a 50 mg dose of sitagliptin phosphate monohydrate, with encouraging results. Thus it can be concluded that the aim of the research: spherical crystallization of sitagliptin phosphate monohydrate for the formulation of directly compressible tablets is fulfilled.

INTRODUCTION: Among all the dosage forms that exist today and were existing in the past, the tablet is the most popular dosage form being the most convenient dosage form. Tablets can be made by well-established compression and granulation technology. The world over the machinery needed for tablet compression is well developed.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(5).2082-92

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(5).2082-92

Automation and multiple compression machines can produce thousands of tablets in one minute. Various tooling and excipients and super-disintegrating agents have given a lot of liberty in designing different types of tablet dosage forms.

Further, the tablet can be coated to mask the taste, enhance the appearance, and can be made to disintegrate at a site other than the stomach. This also makes tablets the most popular dosage form. All the APIs that exist today in the world, at least 90 % of them are available in tablet dosage form [1]. This speaks about the popularity and importance of tablet dosage form. The bulk properties of the API, such as bulk density, tapped density, flowability,

compressibility, are very important in order to convert them into tablets. For every single API, in order to be developed into tablet dosage form, bioavailability by the oral route is a must. So, if the bulk properties of drug supports, it is easy to make it into a tablet dosage form. Some of the physical properties of a drug such as a needle/plate shaped crystals do not support free flowability. So, it becomes mandatory to convert them into granules and modify their bulk properties, then suitably convert them into tablets. Granulation technology, though, is the greatest tool for converting any non-compressible powers into compressible; it has its own limitations like the involvement of a granulating agent, wetting of the powders, drying rate, and degradation due to heat. Every API is not directly compressible, and also all excipients are not directly compressible, so direct compression and dry granulation cannot be a remedy alternative always for such APIs. Here lies the importance of spherical crystallization.

The Pharmaceutical industry is looking for easy and more commercial angles of converting APIs into Tablets. The automation in the areas like pelletization, spheronization, extrusion has given wonderful ways of converting APIs into directly compressible spherical agglomerates. Along with these techniques, one can also take the help of co-crystallization, co-precipitation, co-agglomeration. So, the use of API, along with directly compressible excipients, has regulated this field. Among all these areas, there is also an area that is important in this regard, which is a method of crystallization itself: spherical crystallization [2].

Spherical crystallization is the technique that uses solvent and anti-solvent along with bridging liquid so that the drug particles are allowed to come out of mother liquor and stick to each other to become spherical agglomerates /spherical crystals. When such drug particles are obtained in the bulk drug industry, the API gets converted into Spherical crystals at the beginning stages. This becomes a handy powder of API to be directly converted into tablet dosage form by skipping the granulation stage. One can use any other directly compressible (diluent) excipient along with API, and together the mixture becomes directly compressible [3]. Under this research, API - Sitagliptin phosphate monohydrate was targeted for spherical crystallization because although directly compressible, is not very free-flowing. The project was undertaken to see that the technique of spherical crystallization, which worked wonderfully on benzoic acid, salicylic acid, and aspirin, works for Sitagliptin phosphate monohydrate. Spherical crystallization can improve bulk properties of API, namely flowability, and can also get better compressed than API. Sitagliptin phosphate monohydrate is crystalline non-free-flowing power. It is mandatory to convert this powder into granules in order to make it flow to the compression cycle. Sitagliptin phosphate monohydrate is a DPP-4 inhibitor. It is fast running anti-diabetic molecule [4]. By converting it into spherical crystals, time of granulation can be saved, which can reduce the cost of production of tablets, and thus there can be commercial applications to such attempts.

MATERIALS AND METHODS:

Pre-formulation Evaluation: Pure Sitagliptin phosphate monohydrate powder was evaluated for organoleptic properties (Colour, odor, appearance and appearance under the microscope), melting point, and determination of solubility, UV spectroscopy, differential scanning calorimetry studies and infrared spectroscopy [5].

Trial Batches for Spherical Crystallization of Sitagliptin Phosphate Monohydrate:

Batch 1: 1 gm sitagliptin phosphate monohydrate was dissolved in 20 mL of distilled water. The clear solution obtained was mixed with 80 mL ethanol and stirred at 600 rpm using four blades overhead stirrer (Remi make). 3 mL chloroform was added as bridging liquid into it. Stirring was continued for 20 min. The mixed solution was filtered to obtain spherical agglomerates.

Batch 2: 0.5 gm sitagliptin phosphate monohydrate was dissolved in 10 mL of distilled water. The clear solution obtained was mixed with 60 mL ethanol and stirred at 600 rpm using a four-blade overhead stirrer (Remi make). 3 mL chloroform was added as bridging liquid into it. Stirring was continued for 20 min. The mixed solution was filtered to obtain spherical agglomerates.

Batch 3: 0.5 gm sitagliptin phosphate monohydrate was dissolved in 15 mL of distilled water. The clear

solution obtained was mixed with 60 mL ethanol and was stirred at 600 rpm using four blades overhead stirrer (Remi make). 4 mL chloroform was added as bridging liquid into it. Stirring was continued for 20 min. The mixed solution was filtered and evaporated on a hot water bath till half quantity evaporated. This solution was kept for cooling in the refrigerator at 4 ºC overnight to obtain spherical agglomerates.

Batch 4: 0.5 gm Sitagliptin phosphate monohydrate was dissolved in 15 mL of distilled water. Afterward, this clear solution obtained was mixed with 60 mL ethanol and was stirred at 800 rpm using four blades overhead stirrer (Remi make). During stirring temperature of 5 ºC was maintained, and 2 mL chloroform was added as bridging liquid into it. Stirring was continued for 20 min. The mixed solution was filtered to obtain agglomerates.

Batch 5: 1 gm Sitagliptin phosphate monohydrate was dissolved in 20 mL of distilled water. The clear solution obtained was mixed with 80 mL ethanol and was stirred at 800 rpm using a four-blade overhead stirrer (Remi make). 4 mL chloroform was added as bridging liquid into it. Stirring was continued for 20 min. The mixed solution was filtered to obtain spherical agglomerates.

Batch 6: 1 gm of Sitagliptin phosphate monohydrate was dissolved in 15 mL of distilled water. The clear solution obtained was mixed with 60 mL ethanol and was stirred at 800 rpm using four overhead blade stirrer (Remi make). 6 mL chloroform was added as bridging liquid into it. Stirring was continued for 30 min. The mixed solution was filtered to obtain spherical agglomerates.

Batch 7: 2 gm of Sitagliptin phosphate monohydrate was dissolved in 30 mL of distilled water. Clear solution obtained was mixed with 150 mL ethanol and mixed at 800 rpm using four-blade overhead stirrer (Remi make). 10 mL chloroform was added as bridging liquid into it. Stirring was continued for 30 min. Mixed solution was filtered to obtain spherical agglomerates [6, 7]. This Experiment was further continued even after 7th batch gave good results . This batch was taken as central reference batch and a factorial design was developed around it.

Factorial Design: Optimization: -A two factor, three levels 3^2 full factorial design opted for the optimization of variables. A factorial design is an efficient method of finding the relative significance of a number of variables and their interaction on the response or outcome of the study. The response surface method is a useful and efficient tool to obtain an appropriate model with minimum excipients. Optimization procedure involving factorial designs and analysis of response surface is powerful, efficient, and also a systematic tool and usually used in developing different oral dosage formulations. In this work, the factorial design was used to optimize the concentrations of ethanol (bad solvent) and chloroform (bridging liquid). A two factor, three levels 3^2 full factorial design was used, and nine experimental runs were performed. Statistical models with interaction terms were derived to evaluate the influence of Ethanol (X1) and Chloroform (X2) on yield (Y1) and Carr's index (Y2).

Full Factorial Design: A 3^2 randomized factorial design was adopted to optimize the variables. In this design, two factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amount of Ethanol (X1) and Chloroform (X2) were chosen as independent variables. Yield (Y1) and Carr's index (Y2) were selected as the dependant variables. The formulations and Evaluation of factorial batches (OP1 to OP9) is shown in the table. The following statistical model incorporating interactive and polynomial terms was used to evaluate the responses:-

$$Y = \beta0 + \beta1X1 + \beta2X2 + \beta12X1X2 + \beta11X12+\beta22 X22 \quad (1)$$

Where Y is the dependent variable, β0 is the arithmetic mean response of the 9 runs, and β1 and β2 are the estimated coefficients for the factors X1and X2 respectively. The main effects (X1 and X2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X1 X2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X1 2 and X22) are included to investigate nonlinearity.

The multiple regression analysis was performed, followed by ANOVA to identify insignificant

variables. Mathematical modeling, evaluation of the ability to fit the model, and response surface modeling were performed with Design-Expert software. A factor is considered to influence the response if the effects significantly differ from zero and the p-value is less than 0.05. The low value of $P<0.05$ and a high value of R^2 (Correlation coefficient) >0.9 indicate excellent goodness of fit. To confirm the omission of non-significant terms, an F statistic was calculated after applying the analysis of variance for the full model and the reduced model. The equations represent the quantitative effect of factors (X1 and X2) upon the responses (Y1 and Y2). Coefficients with one factor represent the effect of that particular factor, 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. A positive sign in front of the terms indicates a synergistic effect, while a negative sign indicates the antagonistic effect of factors [8, 9].

TABLE 1: DESIGN MATRIX AS PER 3^2 FACTORIAL DESIGNS

Batch code	Factor with coded levels		Actual values	
	Ethanol	Chloroform	Yield	Carr's index
	X1	X2	%	%
F1	-1	-1	63	26.66
F2	-1	0	60	29.03
F3	-1	+1	68	31
F4	0	-1	41.5	25.80
F5	0	0	56.5	21.87
F6	0	+1	74	19.44
F7	+1	-1	97.5	18.42
F8	+1	0	94.5	17
F9	+1	+1	83	20.51

TABLE 2: INDEPENDENT VARIABLES AND LEVELS USED FOR FACTORIAL DESIGN

Independent variable, factor	Level used		
	-1	0	+1
X1 :Ethanol	140 mL	150 mL	160 mL
X2 : Chloroform	5 mL	10 mL	15 mL

TABLE 3: DEPENDENT VARIABLES USED IN FACTORIAL DESIGN

Code	Dependent variables
Y1	Yield (%)
Y2	Carr's index (%)

Characterization of Optimized Batch: The optimized batch was characterized by scanning electron microscopy, X-Ray diffraction of raw crystals, spherical crystals, and microscopic study using a polarized microscope.

Pre-compression Study of Raw Crystals and Spherical Crystals of Sitagliptin Phosphate Monohydrate: % Compressibility / Carr's index was determined as per the following formula of raw crystals and spherical crystals [6].

$$\text{Carr's compressibility Index (\%)} = [(TD - BD)/TD] \times 100$$

Where; TD = Tapped Density, BD = Bulk density

Compression of Spherical Crystals to Tablet Dosage Form [E]: This study was performed to find out the difference of hardness between tablets created from raw crystals and spherical crystals of Sitagliptin phosphate monohydrate under the same compression pressure. In this raw crystals and spherical crystals with 1% magnesium stearate (as a lubricant) were compressed at the same compression pressure, and then the difference in hardness of both tablets was checked. The tablets were prepared by direct compression method on a rotary tablet compression machine by compressing crystal blend with magnesium stearate as lubricant and sodium starch glycolate as disintegrant. All the powder blends for the preparation of tablets were accurately weighed as per formulae and individually filled in the die cavity of 10.5 mm concave-shaped punch. Compression was done at constant pressure. The hardness thus obtained was determined.

TABLE 4: FORMULA FOR TABLET CONTAINING 65 MG OF SITAGLIPTIN PHOSPHATE MONOHYDRATE (EQUIVALENT TO 50 mg OF SITAGLIPTIN)

S. no.	Ingredients	Quantity
1	Sitagliptin phosphate monohydrate (Spherical crystals)	65 mg
2	Microcrystalline cellulose	35 mg
3	Magnesium stearate	1% w/w
4	Sodium starch gluconate (SSG)	8% w/w
		Total wt.=109 mg

Evaluation and Comparison of Tablet (E) With Marketed Formulation: Directly compressed tablet (E) was evaluated for appearance, hardness, friability, weight variation, disintegration time, and *in–vitro* drug release kinetics. The Drug release study was carried out using:

Dissolution apparatus : USP Type II (Paddle)
Dissolution medium : 6.8 PH buffer

Speed of paddle	:	75 rpm
Sample withdrawn	:	5.0 mL
Temperature	:	Temperature: 37 ± 0.5 ºC

The release rate of Sitagliptin phosphate mono-hydrate (E) and the film-coated marketed tablet was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 mL of 6.8 pH buffer, at 37 ± 0.5 °C and 75 rpm. A, 5 mL sample solution was withdrawn from the dissolution apparatus after each 10 min for 2 h. Samples were replaced by its equivalent volume of dissolution medium. The sample solutions were filtered through Whatman filter paper (45 µm), from this filtered solution, 0.5 mL solution was taken into 10 mL volumetric flask and volume was made up with 6.8 pH buffer and solutions were analyzed at 267 nm by UV Spectrophotometer. The release in the dissolution medium was determined by software (PCP disso v 2.08). The tablet E was coated because of marketed tablet available, that contains 65 mg sitagliptin phosphate monohydrate, is a film-coated tablet. For correct comparison of the dissolution rate and % drug release of both tablets, the coating was applied to tablet "E" using ethyl cellulose as seal coat followed by a coating of HPMC 2910.2% solution of ethyl cellulose was made in ethanol and tablet was dipped and dried. This procedure was repeated 5 times. Then HPMC 2910 (5% in ethanol) was taken as the main film coat, and the tablet was dipped into it at 3 times and dried. Weight increased due to coating was found to be 5 mg.

RESULTS AND DISCUSSION:

Pre-formulation Evaluation: The sample of Sitagliptin phosphate monohydrate was found to be white, odorless crystalline powder. Image of sitagliptin Phosphate Monohydrate under polar-izing microscope: Showing needle-like crystals [11].

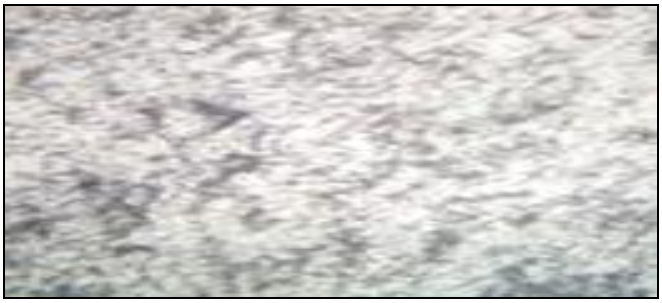

FIG. 1: IMAGE OF SITAGLIPTIN PHOSPHATE MONOHYDRATE UNDER POLARIZING MICROSCOPE

Melting Point: The melting point of sitagliptin phosphate monohydrate was found to be in the range of 216 ºC - 218 ºC.

Determination of Solubility: The saturated solubility of sitagliptin phosphate monohydrate was observed in distilled water [12].

TABLE 5: SOLUBILITY DATA OF SITAGLIPTIN PHOSPHATE MONOHYDRATE

Solvent	Solubility(µg/mL)
Distilled water	50 µg/mL

UV-spectroscopy (Determination of λ_{max}): Wavelength of maximum absorbance (λ_{max}) of sitagliptin phosphate monohydrate was found to be 267 nm in distilled water [13].

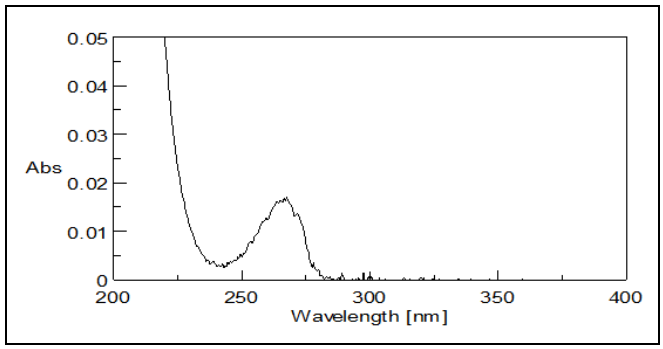

FIG. 2: UV SPECTRUM OF SITAGLIPTIN PHOSPHATE MONOHYDRATE

Calibration Curve for Sitagliptin Phosphate Monohydrate: The calibration curve for sitagliptin phosphate monohydrate in distilled water is shown in **Fig. 3**. The graph of absorbance *vs.* concentration for sitagliptin phosphate monohydrate was found to be linear in the concentration range of 0-10 µg/mL at 267 nm. The R^2 of the calibration curve was found to be 0.999, which concludes that it follows the Beers Lambert's law within this concentration range [13].

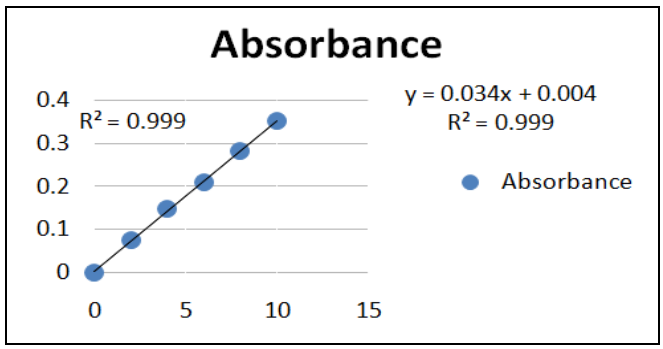

FIG. 3: CALIBRATION CURVE OF SITAGLIPTIN PHOSPHATE MONOHYDRATE

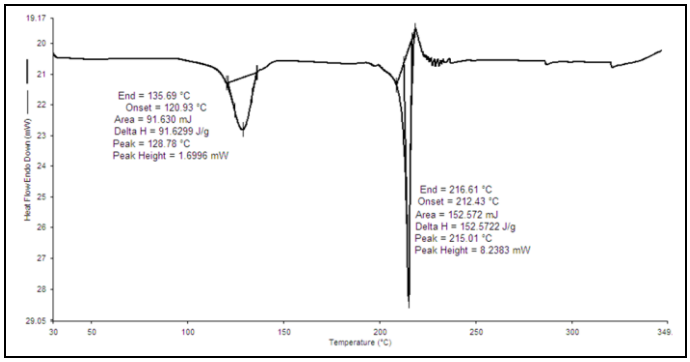

FIG. 4: DSC OF SITAGLIPTIN PHOSPHATE MONOHYDRATE

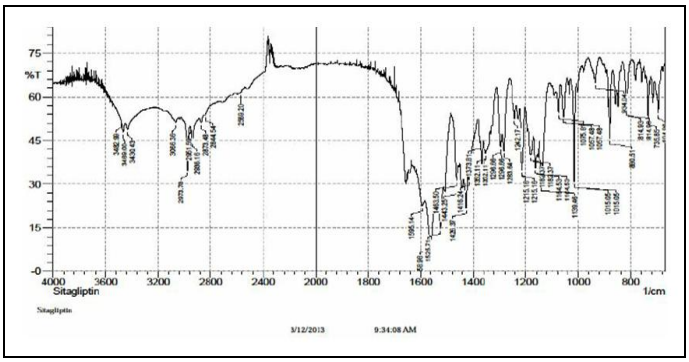

FIG. 5: FTIR GRAPH OF SITAGLIPTIN PHOSPHATE MONOHYDRATE

Differential Scanning Calorimetric Studies: Sitagliptin phosphate monohydrate differential scanning calorimetry studies indicated a sharp peak at 216.61 °C, corresponding to the melting of pure sitagliptin phosphate monohydrate. So, it was inferred that the given sample of the drug was pure. The DSC thermogram of Sitagliptin phosphate monohydrate showed a characteristic sharp endothermic peak at 135.69 ºC due to water liberation from the drug as it is a monohydrate salt.

Infrared Spectroscopy: The FTIR spectrum of the API shown in **Fig. 5** and interpretation of FTIR spectra is given in **Table 6** FTIR spectrum of sitagliptin phosphate monohydrate showed all peaks corresponding to functional groups present in the structure of sitagliptin phosphate monohydrate.

Trial Batches for Spherical Crystallization of Sitagliptin Phosphate Monohydrate and Optimized Batch from Trial Batches Study: Among all 7 batches, the 7th batch was found to have best results.

TABLE 7: TRIAL BATCH NO. 7

S. no.	Ingredients	Quantity
1	Water	30 mL
2	Sitagliptin phosphate monohydrate	2.0 gm
4	Ethanol	150 mL
5	Chloroform	10 mL

FIG. 6: SPHERICAL CRYSTALS OF TRIAL BATCH NO. 7

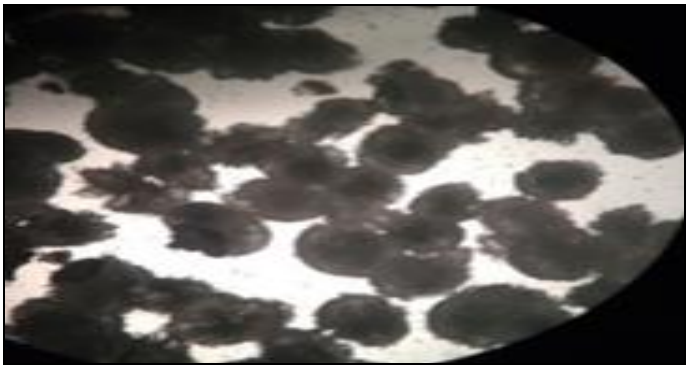

FIG. 7: IMAGE OF SPHERICAL CRYSTALS OF TRIAL BATCH NO. 7 UNDER POLARIZING MICROSCOPE

Factorial Design: A full factorial design was applied, taking into consideration above Trial batch No. 7 as a best batch (as zero levels). Three levels of each of the two factors: concentration of Ethanol and concentration of Chloroform were adopted for further investigation as required by the design, and the factor levels were suitably coded, as indicated in **Table 11**. Based on the results of the preliminary study, the concentration of Ethanol (X1) and Concentration of Chloroform (X2) were chosen as independent variables in a 3^2 full factorial design. The Yield (Y1) and Carr's index of the obtained crystals-Y2) were selected as the dependent variables. The data **Table 8** and **9** clearly indicate that Yield and Carr's index are strongly dependent on the selected independent variables.

TABLE 8: DEPENDENT VARIABLES USED IN FACTORIAL DESIGN

Code	Dependent variables
Y1	Yield (%)
Y2	Carr's index (%)

TABLE 9: DESIGN MATRIX AS PER 3^2 FACTORIAL DESIGNS

Std	Run	Factor 1 A-Bad solvent	Factor 2 B-Bridging liquid	Response 1 R1 yield	Response 2 R2Carr's index
7	1	-1	1	68	31
2	2	0	-1	41.5	25.8
5	3	0	0	56.5	21.87
4	4	-1	0	60	29.03
8	5	0	1	74	19.44
6	6	-1	0	94.5	17
1	7	-1	-1	63	26.6
3	8 Optimized Batch	1	-1	97.5	18.42
9	9	1	1	82	20.51

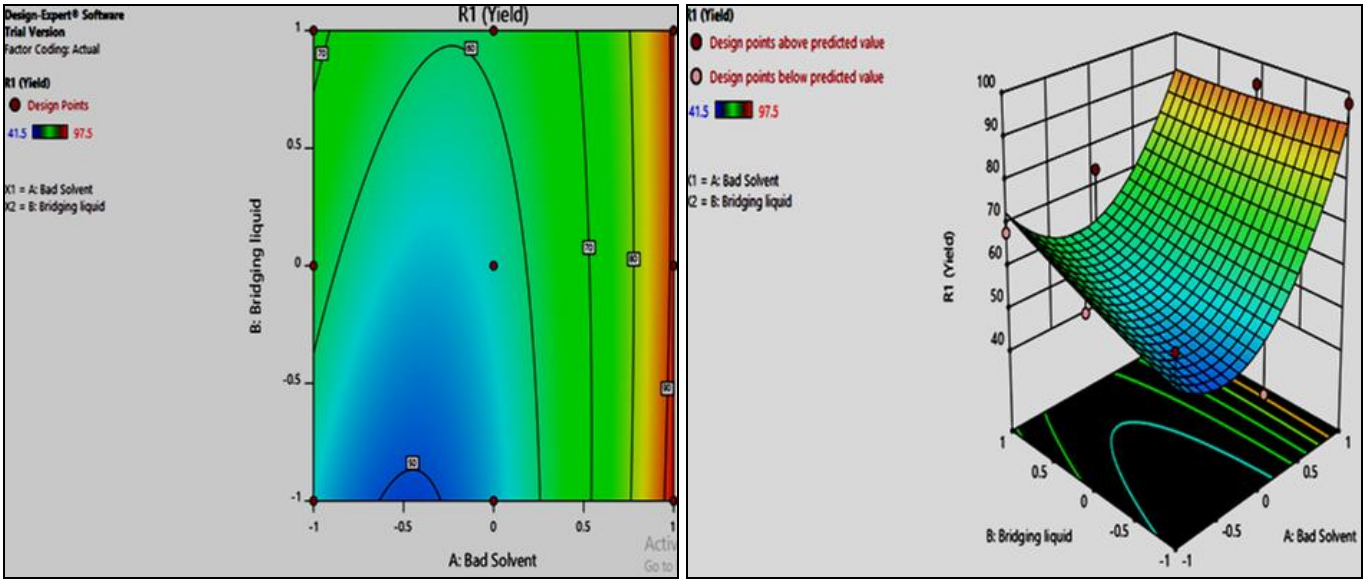

FIG. 8: THE RESPONSE SURFACE GRAPH FOR % YIELD

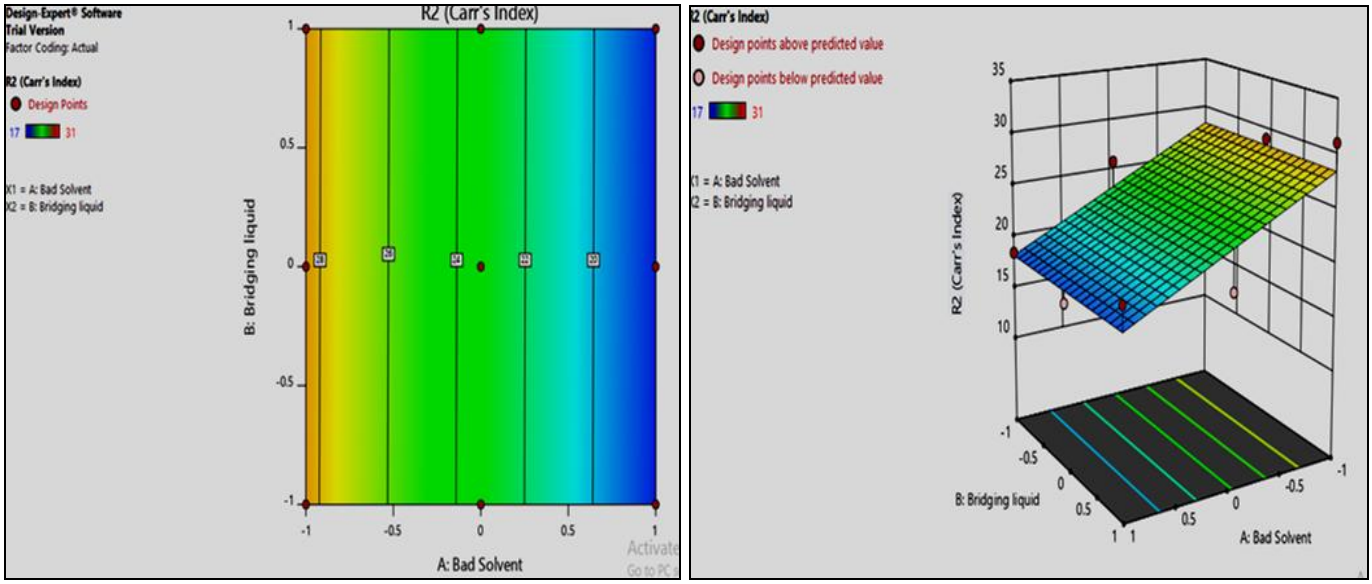

FIG. 9: THE RESPONSE SURFACE GRAPH FOR % CARRS'S INDEX

TABLE 10: RESPONSE SUMMARY FOR OPTIMIZES (SUGGESTED) BATCH

Name	units	Type	Changes	Std.Dev	Low	High
Bad solvent		Factor	Easy	0	-1	1
Bridging liquid		factor	Easy	0	-1	1
R1	Yield	Response		12.8372	41.5	97.5
R2	Carr's index	Response		2.5952	17	31

Characterization of Optimized Batch-A] Scanning Electron Microscopy: SEM analysis of optimized spherical crystals from Batch shows morphology like below [13]

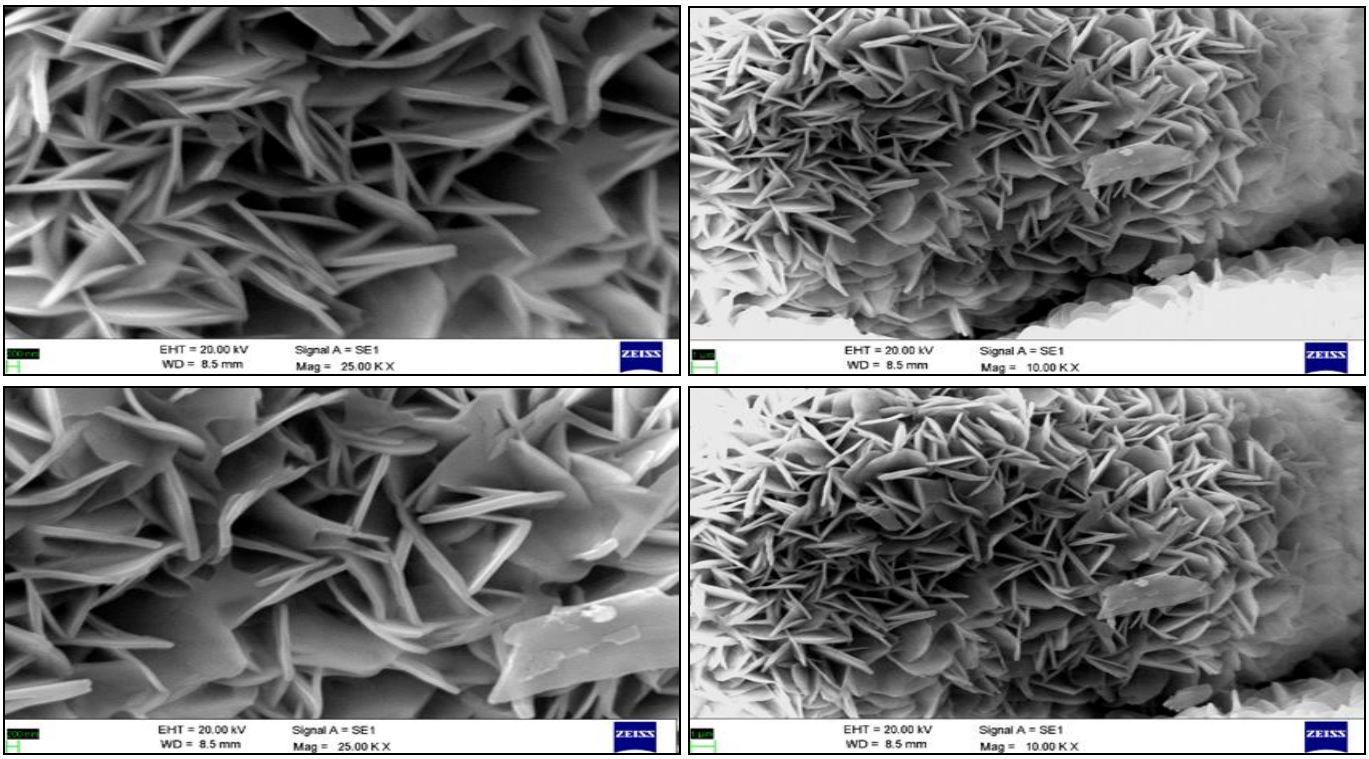

FIG. 10: SEM IMAGE OF SITAGLIPTIN PHOSPHATE MONOHYDARTE SPHERICAL CRYSTALS AT INCREASED MAGNIFICATION

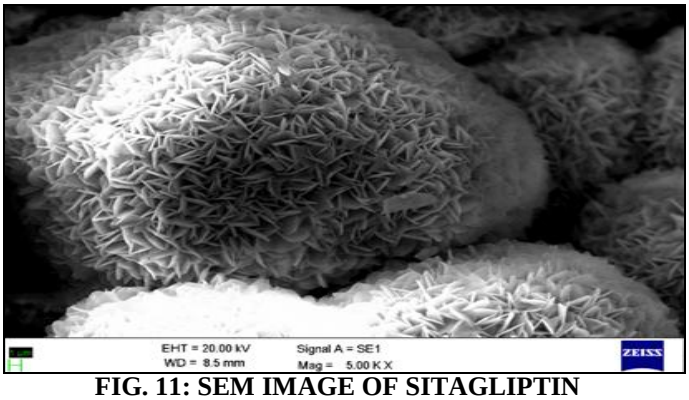

FIG. 11: SEM IMAGE OF SITAGLIPTIN PHOSPHATE MONOHYDARTE SPHERICAL CRYSTALS AT MODERATE MAGNIFICATION

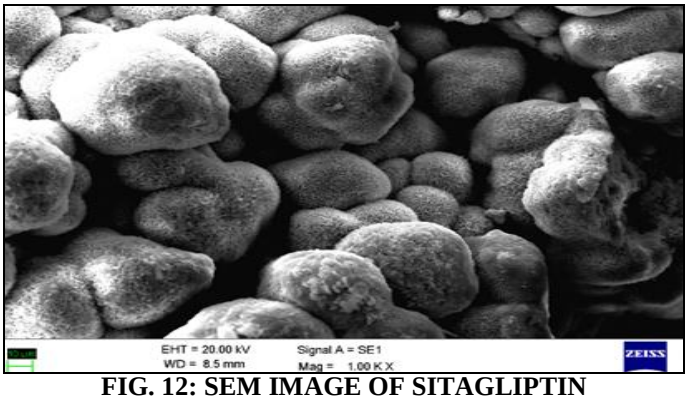

FIG. 12: SEM IMAGE OF SITAGLIPTIN PHOSPHATE MONOHYDARTE SPHERICAL CRYSTALS AT LOWER MAGNIFICATION

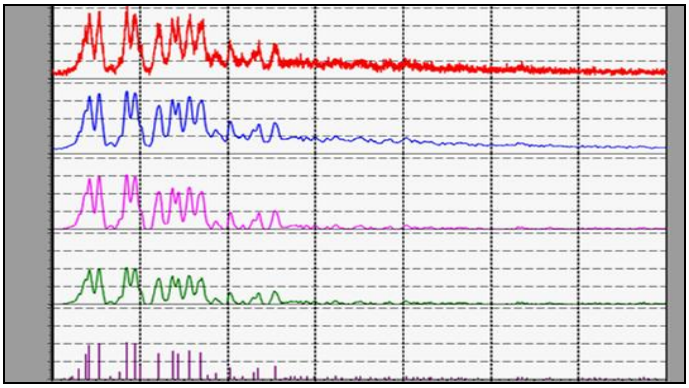

FIG. 13: XRD GRAPH OF RAW CRYSTALS OF SITAGLIPTIN PHOSPHATE MONOHYDRATE

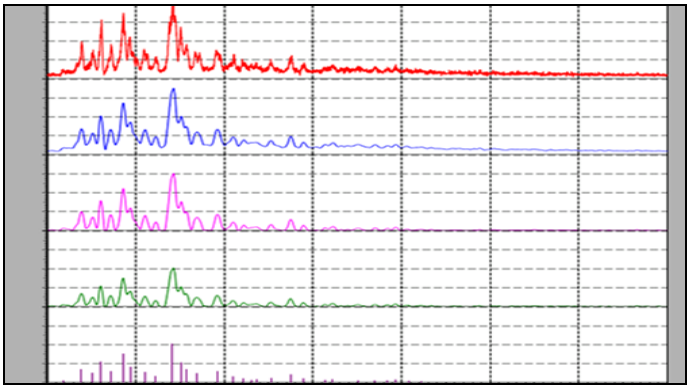

FIG. 14: XRD GRAPH OF SPHERICAL CRYSTALS OF SITAGLIPTIN PHOSPHATE MONOHYDRATE

X-Ray Diffraction (XPRD) of Raw Crystals and Spherical Crystals of Sitagliptin Phosphate Monohydrate: XRPD of raw crystals and spherical agglomerates of sitagliptin phosphate monohydrate are shown in **Fig. 13** and **14**. It has been observed that the XRPD of raw crystals and all spherical agglomerates were the same, which has indicated that polymorphic change has not occurred during spherical crystallization [12]. Also, the X-Ray diffraction (XRD) of spherical crystals is slightly smooth owing to its spherical arrangement.

Polarized Microscopic Study: Images of spherical crystals of sitagliptin phosphate monohydrate were observed under the polarizing image microscopy. The crystals appeared spherical and systematically arranged and shining [12].

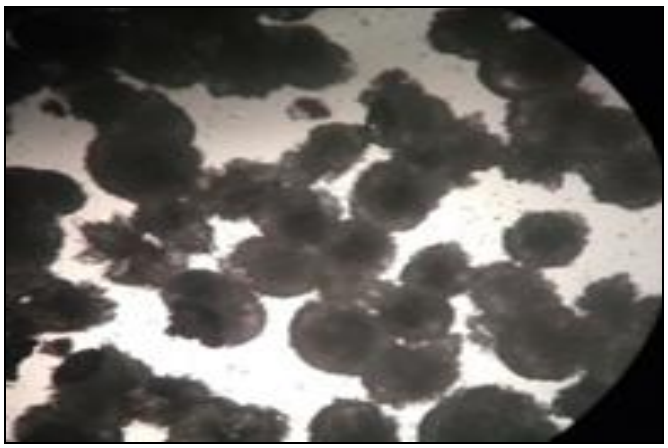

FIG. 15: POLARIZED MICROSCOPIC IMAGES OF SPHERICAL CRYSTALS

Pre-compression Study of Raw Crystals and Spherical Crystals of Sitagliptin Phosphate Monohydrate:

Compressibility Index: Carr's compressibility Index (%) of raw crystals was found to be 27.71% [12]. Carr's compressibility Index (%) of spherical crystals was found to be 17%.

Compression of Spherical Crystals to Tablet Dosage Form [E]: When sitagliptin phosphate monohydrate was made into spherical crystals, it became free-flowing. Spherical crystals produced more hard tablets than raw crystals at the same compression pressure.

It concludes that by converting raw crystals into the spherical crystals, low compression pressure was needed to make tablets and spherical crystals were easy to compress than the raw crystals.

TABLE 11: COMPARISON OF TABLET HARDNESS OF RAW CRYSTALS AND SPHERICAL CRYSTALS OF SITAGLIPTIN PHOSPHATE MONOHYDRATE [13, 14]

S. no.	Compression pressure (Ton)	Raw crystal tablet hardness (Kg)	Spherical crystal's tablet hardness (Kg)
0	6	1	1.5
1	6.5	1.5	2.5
2	7.0	2.5	3.5
3	7.5	4	5
4	8	4	5

Evaluation and Comparison of Tablet (E) with Marketed Formulation:

1. Appearance: The tablets were observed visually and did not show any defects such as capping, chipping, and lamination.

2. Hardness of the Tablets: the hardness of tablets was determined using Monsanto hardness tester. It was found in the range of 4.0 to 5.0 kg/cm^2. Hardness values were satisfactory and indicated good mechanical strength of tablets.

3. Friability of the Tablets: Percentage weight loss (friability) of the tablets of each formulation was measured and was found to be less than 1.0%.

4. Weight Variation of the Tablets: Tablets showed uniformity of weight as per I. P. limits. The individual weight of 20 tablets was found to be 102 mg to 108 mg.

5. Disintegration Time: Disintegration time of marketed film coated tablet was found to be: 1 min 14 sec. Disintegration time of tablet "E" was found to be: 1 min 48 sec.

***In-vitro* Dissolution Studies:** [15]

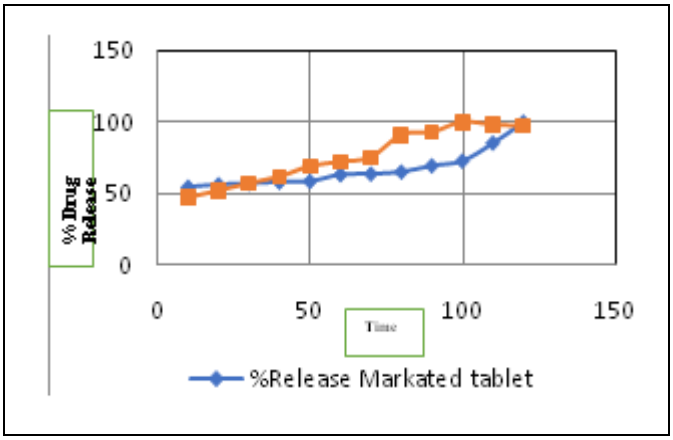

FIG. 16: COMPARISON OF DISSOLUTION STUDY OF MARKETED AND COATED TABLET (E)

From the dissolution study, it concludes that the marketed tablet shows 100% release in 120 min, and the coated tablet E shows 97% drug release in 120 min, which is comparable.

TABLE 12: DISSOLUTION STUDY OF MARKETED TABLET AND FILM-COATED TABLET (E)

Time minutes	Absorbance	% Drug release (Marketed)	Absorbance	% Drug release (Sample E)
10	0.4511	46.91	0.3640	54.14
20	0.4980	51.79	0.3761	55.94
30	0.5411	56.99	0.3804	56.58
40	0.5928	61.65	0.3873	57.60
50	0.6630	68.95	0.3913	58.20
60	0.6928	72.05	0.4230	62.91
70	0.7572	75.22	0.4264	63.42
80	0.8702	91	0.4357	64.80
90	0.8902	92.58	0.4653	69.21
100	0.9615	100	0.4879	72.57
110	0.9423	98.00	0.5227	85.18
120	0.9398	97.24	0.6723	100

SUMMARY AND CONCLUSION: Sitagliptin was invented in 2006 as a DPP-4 inhibitor. It is soluble in water to the extent of 0.03 mg/ml as thus affected bioavailability problems. Soon it was converted into phosphate monohydrate salt with solubility 50 mg/ml, which solved its bioavailability problem. In this research, an attempt is made to convert it from its crystalline form into spherical crystals. Spherical crystals have bulk properties that can be adapted to direct compression tableting. This kind of innovation saves the time needed for granulation since the API is available in spherical crystals, just by adding lubricant and disintegrant, it can be directly compressed.

In the marker tablets of sitagliptin phosphate monohydrate are available and it is a product in demand for management of type II diabetes. Any API, which is crystalline, can be made to adapt for direct compression tablet technology with various methods. One of such method which converts APIs into directly compressible and free-flowing particles is spherical crystallization. In this research sitagliptin, phosphate monohydrate was made as spherical crystals using water as a solvent, ethanol as anti-solvent, and chloroform as bridging liquid. 3^2 factorial designs for optimization was applied to get an optimized batch with a concentration of bridging liquid and anti-solvent as independent and Carr's index and % yield as dependant variables. Batch F 7 was considered optimized with a yield of 97.5%. Spherical crystals then obtained were characterized using X-Ray diffraction, SEM, % compressibility, and flowability. The spherical crystals were directly compressed by adding 8% SSG and 2% magnesium stearate into a tablet with a total weight of 109 mg containing 65 mg of sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin. The resultant tablets were film-coated using HPMC 2910. It was compared with marketed film-coated tablet, both having a dose equivalent to 50 mg of sitagliptin.

The results were encouraging thus, it can be concluded that the aim of the research: Spherical crystallization of sitagliptin phosphate monohydrate for the formulation of directly compressible tablets is fulfilled.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Pande V: An overview on emerging trends in immediate release tablet technologies. Austin Therapeutics 2016; 3: 1026.
2. Reddy B: Improved tablet production by modified granulation techniques-a review. Int Journal of Research in Pharmacy and Life Sciences. 2014; 2: 224-35.
3. Tiwari S and Verma P: Spherical crystallization. a novel drug delivery system. Int Journal of Pharmacy & Life Sciences 2011; 2(9).
4. https://www.medindia.net/drug-price/sitagliptin/januvia-100mg.htm. (Accessed on June 5 ,2019)
5. Ravisankar P and Mounika G: A simple validated UV Spectrophotometric method for quantitative analysis of Sitagliptin phosphate in the pharmaceutical dosage form. J of Chemical and Pharmaceutical Sciences 2014; 7: 254-8.
6. Kawashima Y and Imai M: Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. Powder technology 2003; 130 (1-3): 283-9.

7. Polowczyk, Izabela, Szczesniak and Karolina L: Spherical agglomeration of acetylsalicylic acid. E3S Web of Conferences 2016; 8: 01018. Paradkar AR, Pawar AP, Chordiya JK, Patil VB and Ketkar AR: Spherical Crystallization of Celecoxib. Drug Development and Industrial Pharmacy 2002; 28(10) 1213-20.
8. https://www.statease.com/software/design-expert/
9. Kawashima Y and Cui F: Parameters determining the agglomeration behaviour and the micromeritic properties of spherically agglomerated crystals prepared by the spherical crystallization technique with miscible solvent systems. Int J of Pharmaceutics 1995; 119(2): 139-47.
10. Stofella NCF, Veiga A and Oliveira LJ: Solid-state characterization of different crystalline forms of sitagliptin, Materials 2019; 12: 2351.
11. https://www.medindia.net/drug-price/sitagliptin/januvia-100mg.htm.(accessed on jun 5, 2019)
12. Patel S, Aditya K and Arvind B: Compression physics in the formulation development of tablets. Critical Reviews in Therapeutic Drug Carrier Systems 2006; 23(1): 1-65.
13. Nguyen, Thanh, Morton, David and Karen H: Predicting tablet strength from the wet granulation conditions *via* the unified compaction curve. Procedia Engineering 2015; 102: 517-26.
14. Sekaran CB and Rani AP: Development and validation of spectrophotometric method for the determination of DPP-4 inhibitor, sitagliptin, in its pharmaceutical preparations. Eclética Química 2010; 35(3): 45-53.

How to cite this article:
Singh MC and Loharkar RR: Spherical crystallization of sitagliptin phosphate monohydrate for formulation of directly compressible tablets. Int J Pharm Sci & Res 2020; 11(5): 2082-92. doi: 10.13040/IJPSR.0975-8232.11(5).2082-92.