A QBD APPROACH TO IMPROVEMENT OF SOLUBILITY AND BIOAVAILABILITY OF IVACAFTOR BY SPRAY DRYING TECHNOLOGY: INVITRO AND INVIVO EVALUATION

Purnachandra Reddy Guntaka[1]*, Srinivas Lankalapalli[2], Dr. Ravi Kumar Kota[3]

Abstract

Objective: The present investigation was aimed to overcome the problems associated with the solubility, dissolution and oral bioavailability of ivacaftor by employing spray drying technology.

Method: Ivacaftor solid dispersions were prepared by using copovidone, hypromellose 5CPs, soluplus were selected as a carriers and sodium lauryl sulphate was selected as surfactant. Drug and polymer ratio was chosen as 1:1 ratio and characterized the solid dispersions by differential scanning calorimetry (DSC), scanning electron calorimetry (SEM) and X-ray diffraction studies (X-RD), Fourier transform infrared spectroscopy (FT-IR) . Later solid dispersions were manufactured into tablets by direct compression method by using Ac-di-sol as a super disintegrant and evaluated for their post compression parameters. Further optimization was done by employing the 2^2 full factorial design by selecting the copovidone (X1) and sodium lauryl sulphate (X2) as independent factors and *invitro* drug release (Y2) as a dependent factor. In addition the optimized formulation was carried out for its *invivo* evaluation by using rats.

Results: Spray drying technology successfully employed to overcome the solubility problem by preparing the drug into their solid dispersions.DSC, SEM, X-RD and FT-UR performed on solid dispersion showed that ivacaftor existed in the amorphous form within the solid dispersion formulation fabricated using the spray drying process. Further design expert 12 software used to find the significant effect of independent factors on dependent factor by using 2D and 3D plots. Moreover, *invivo* study in rats also justified the improvement in the therapeutic efficacy of optimized formulation over pure drug.

Conclusion: Thus, spray-dried technology can be an effective method for enhancing the bioavailability of ivacaftor.

Keywords: Copovidone, Ivacaftor, Soluplus, Spray drying and sodium lauryl sulfate

[1*,2]GITAM Institute of Pharmacy, GITAM University, Visakhapatnam, India.
[3]Professor & H.O.D. Department of Pharmaceutics, Santhiram College of Pharmacy NH-40 Nerawada Nandyal-518501

Corresponding Author: - Purnachandra Reddy Guntaka
GITAM Institute of Pharmacy, GITAM University, Visakhapatnam, India. E-mail: gpcreddy86@gmail.com

DOI: 10.48047/ecb/2023.12.si5a.0408

Introduction:

The solubility of poorly soluble drugs is the major challenge in the development of novel formulations[1]. Number of technologies was used in the development of formulations. In those one of the technology is preparation of solid dispersions used by spray drying (SDY) technology. SDY technique is most effective and commonly used for the enhancement of solubility and bioavailability of poorly soluble drugs[2].It is a one-step technique that is convenient and reproducible. The primary principle underlying SDY is the continuous conversion of material from liquid to solid state by the use of a heat drying chamber[3]. In this method, the drug and polymer are dissolved in solvent and then sprayed continuously into a heating chamber, where the solvent is evaporated and transformed to solid state [4].

Ivacaftor is a crystalline white off powder used to treat cystic fibrosis. [5]. In aqueous solutions, the crystalline form of the pharmacological compounds is nearly insoluble (0.001 mg/ml). To boost ivacaftor's solubility, solid dispersion technology was chosen[6]. As a result, the polymer carrier must be capable of forming an amorphous solid dispersion with ivacaftor, as well as efivacaftor in an amorphous state[7]. Due to ivacaftor's limited aqueous solubility, an SDY technology is employed to increase its solubility[6].

Quality by design (QbD) is one of the advanced approach in the pharmaceutical industry to optimize the parameters to assure the quality of the final product[8].

In this investigation, Ivacaftor SD were prepared by SDY technology by the help of QbD to improve the solubility and dissolution.

Materials and Methods

Ivacaftor was kindly gifted by Hetero labs, Hyderabad, India. Copovidone, Hypromellose 5cps, Soluplus, Sodium lauryl sulphate, Poloxamer were purchased form the Dow chemical, Mumbai. All solvents and reagents were analytical grade.

Preparation of Solid Dispersions

Ivacaftor 150mg was dissolved in a mixture of acetone and water (90 mL). Then, gradually add Copovidone or Hypromellose 5cps or soluplus while stirring for 20 minutes to dissolve. The sodium lauryl solution was then mixed with distilled water (20 mL)[9]. After 30 minutes of stirring, the final liquid was spray-dried using a tiny spray dryer. The spray drier was started with the intake temperature set to 90°C, the feeding rate set to 3 mL/min, the atomizing air pressure set to 3000 psi, and the nitrogen gas flow set to 600 L/h with 100% aspiration. Prior to analysis, all samples were passed through a 250-m sieve (mesh size 60) and stored at room temperature in a desiccator[10].

Characterization of Ivacaftor solid dispersions

Solubility studies of Ivacaftor solid dispersions

In this process estimation of Ivacaftor were performed by using pure drug and its solid dispersions. Ivacaftor with carriers were shaken for 48 hours. Subsequently, the solution was filtered through a whatman filter paper. Filtered solution of Ivacaftor was analyzed by using UV at maximum absorbance[11].

Scanning Electron Microscopy

The morphology and particle size of ZD, PVP, HPMC, Eudragit S100, and solid dispersions were investigated using a Zeiss EVO 50 Scanning Electron Microscope (SEM) (Oberkochen, Germany). A SEM sample was generated by coating the particles with a thin layer of gold to ensure sufficient conductivity to the sample's surface using a Polaron SC500 sputter coater (Polaron Equipment, Watford, UK) operating under argon. Powdered samples were put on adhesive carbon tape and evaluated in low vacuum mode using a 20 keV acceleration voltage[12].

XRD Analysis

Powder XRD is unique analytical technology used for identification of crystalline material. The instrument used for X-Ray Powder Diffraction System (PANalytical Empyrean) with appropriate data handling system/software.500 mg to 1.0 gm of blend and grind gently to make homogenous powder. Fill the sample holder by pouring the homogenous powder slowly through sides and level gently with the help of a glass slide with minimum disturbance to the bed[13].

DSC Studies

It is a thermal analysis technique in which the heat flow continuously to a sample by measuring the temperature. Instrument used for determination of DSC is Waters TA DSC Q2000. Crash the sample by using motor and pestle then take 2-5 mg of crashed sample place in aluminum lid with 2 pin hole by using parameters: mass flow 50.0 ml/min, Equilibrate at 30^{o}C, Ramp at 10^{o}C/min to 250^{o}C, Isothermal for 1.00 min[13].

FT – IR studies

The spectroscopic studies were carried for pure drug (Ivacaftor) and Final formulation using FTIR

spectrophotometer (M/s. BRUKER, Model Alpha). Potassium bromide pelted method was used for all solid samples[14]. In KBr pellet method prepare the pellets by mixing sample and potassium bromide then record the IR absorption spectra of the test specimen and the corresponding standard over the range of 400 cm^{-1} to 4000 cm^{-1}.

Preparation of tablets

The SDY procedure was used to make solid dispersions of Ivacaftor with Copovidone and surfactants (one set of experiments), Hypromellose 5 Cps with surfactants (second set of trials), and Soluplus with surfactants (third set of trials). The spray dried material from step 1, cellulose Microcrystalline (Avicel pH 102), croscarmellose sodium, and CSD were sieved together and well combined for 15 minutes in a plastic bag. Mg stearate sieved through #60 mesh and manually blended for 5 minutes in step 2. Compressing the material from step 3 required the use of 9.00 mm round shaped punches[15].

Table 1: Composition of Ivacaftor solid dispersions by Spray drying (SDY)

Ingredients (Units)	ISD1	ISD2	ISD3	ISD4	ISD5	ISD6
Ivacaftor (mg)	150.0	150.0	150.0	150.0	150.0	150.0
Copovidone (mg)	150.0	150.0	-	-	-	-
Hypromellose 5cps (mg)	-	-	150.0	150.0	-	-
Soluplus (mg)	-	-	-	-	150.0	150.0
Sodium lauryl sulphate (mg)	15.0	-	15.0	-	15.0	-
Poloxamer (mg)	-	15.0	-	15.0	-	15.0
Acetone (9 parts) (mg)	QS	QS	QS	QS	QS	QS
Purified water (1 parts) (mg)	QS	QS	QS	QS	QS	QS
Total quantity of Spray dried material weight (mg)	315.0	315.0	315.0	315.0	315.0	315.0
Microcrystalline cellulose (Avicel pH 102) (mg)	214.5	214.5	214.5	214.5	214.5	214.5
Croscarmellose sodium (Ac-Di-Sol) (mg)	12.5	12.5	12.5	12.5	12.5	12.5
Colloidal silicon dioxide (Aerosil 200) (mg)	3.0	3.0	3.0	3.0	3.0	3.0
Magnesium stearate (mg)	5.0	5.0	5.0	5.0	5.0	5.0
Total tablet weight (mg)	**550.0**	**550.0**	**550.0**	**550.0**	**550.0**	**550.0**

Physico-chemical characteristics of Ivacaftor SD tablets

Physico chemical characteristics of Ivacaftor SD tablets prepared by SDY. Evaluation of weight variation, hardness, thickness, Friability and disintegration time.

Weight variation test

Twenty tablets were chosen at random, individually weighed, and an average weight was computed. Not more than two individual weights diverged from the average weight by more than the percentage indicated in the table and should not deviate by more than twice that amount[16].

Hardness test

The tablet hardness was determined in triplicate using the monsanto tablet hardness tester. The tablet was held between the instrument's fixed and moveable parts. The scale was slid to align the zero on the scale with the pointer. The adjustable knob was gently turned till the tablet cracked[17].

Thickness

The thickness of prepared tablets was determined by sandwiching the tablet between the hands of vernier callipers and reading the vernier scale. [18].

Friability

Approximately six tablets were dedusted and weighed with care. The tablets were placed in a friability apparatus and rotated 100 times at a speed of 25 revolutions per minute for 4 minutes. The tablets were extracted, cleaned, and weighed [19].

Disintegration Time

The disintegration time was calculated by placing a tablet in each tube and positioning the basket rack so that the tablets remain 2.5cm below the liquid's surface during their upward movement and sink no closer than 2.5cm from the bottom of the beaker[20]. At a frequency of 28 to 32 cycles per minute, a typical motor device is utilized to move the basket assembly containing the tables up and down a distance of 5 to 6 cm. The time taken for all particles to pass through the 10-mesh was then determined.

Drug content

Crush 5 tablets with a motor and pestle to make a powder. To 100 mL of Methanol, dissolve an equivalent strength weight of the drug ingredient. When it came time to analyse it, UV was used to compare the filter and the drug content to the blank filter. After then, the percent drug content was

computed by dividing the actual amount of drug by the theoretical amount.

***In vitro* Dissolution studies**

A Type II dissolving apparatus (labindia) with sinker was used to conduct the experiments, which were carried out at 37°C plus or minus 0.5% C. In order to use the paddle method with a rotation speed of 50rpm and pH 6.8, 900 mL of pH 6.8 sodium phosphate buffer containing 0.7 percent SDS was chosen[21]. The dissolution studies were carried out pH 6.8 sodium phosphate buffer with 0.7% SDS. A 5 ml of sample was withdrawn from the dissolution medium at 5, 10, 15, 20 and 30 minutes and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 255 nm by a UV–visible spectrophotometer. The amount of drug present in the samples was calculated.

Experimental design

After conducting a preliminary feasibility study, a DOE using a full factorial design was carried out in order to optimize the copovidone and SLS concentrations employed in the formulation[22]. The percentage of drug release in 30 minutes was determined to be a critical quality attribute (CQA) of the formulation, and the response ranges were determined based on the dissolution of the formulations. This section explains the study methodology as well as the acceptance criteria. The drug release at 30 minutes was measured using the USP apparatus II (Paddle) at 65 rpm in pH 6.8 sodium phosphate buffer with 0.7 percent SDS in an amount of 900 mL of the solution.

It was necessary to employ a constant tablet weight of 550.00 mg in order to obtain the goal weight, which was achieved by adjusting the quantity with the diluent. Formulation development was carried out with the purpose of selecting the optimal copovidone and SLS concentrations and determining whether there was any interaction between the various variables. The purpose of this study was also to determine the robustness of the proposed formulation. Initially, 22 full factorial Design of Experiments (DOE) with one centre point were investigated, and the findings of the formulation trails done with Design-Expert® 11 Software were compared to the results of the full factorial DOE with one centre point[21], The factors and responses that were investigated and submitted to dissolve testing are summarized in the table below.

Table 2: Design of the 2^2 full factorial Design of Experiments design to study

Factors: Formulation Variables (in mg)		Levels	
		-1	1
A: Copovidone		75	225
B: Sodium lauryl sulphate		7.5	22.5
Responses (in minutes)		Goal	Acceptable Ranges
Y1	Dissolution Time	Minimize	Not Less than 80% Q in 30minutes

***In vivo* Evaluation**

It is possible to determine the ultimate performance of any pharmacological product by conducting in vivo bioavailability tests. A total of nine healthy rabbits (weighing between 2.5 and 3.5kg) were chosen for the pharmacokinetic investigation. The rabbits were starved from 12 hours before the administration of the medicine until 24 hours after the administration of the drug[21]. Throughout the trial, all of the rabbits in both the reference and test groups were provided with unlimited access to water. Each single oral dose of Market product(R) treatment and test (T1) treatment, taken with drinking water, contains 25 mg per kg weight of the patient. Blood samples (600 mL) were drawn from a marginal ear vein at various time intervals (1.2, 3.5, 4, 4.5, 11, 18 and 24 hrs) and were analyzed. Plasma was collected from the blood samples by centrifuging them for 10 minutes at 10,000 rpm for a total of 10 minutes. The 400 L of ethanol was added to the 100 L of plasma to create the final product. To separate the plasma proteins, the liquid was vortexed and centrifuged at 10,000 rpm for 10 minutes at room temperature[23]. The supernatant was evaporated until it was completely dry. The residue was dissolved in 100 liters of ethanol before being used. The concentration of the medication in 20 L of solution was determined by HPLC using a Waters liquid chromatographic system (Model: Alliance 2695) equipped with a quaternary pump, an auto sampler, and an SDY-M30A detector (M/s. Waters, Milford, CT, USA), as previously described. For the analysis, a waters C8 column (150 mm 3.9 mm ID, 5 m) at 30 °C with a 5 m pore size was utilized[24].The protocol for the animal study was approved by the Institute of Animal Ethics Committee (IAEC; Reg. No: CPCSEA/1657/ IAEC/ CMRCP/COL-18/73).

Results & Discursion

The SDY method was used to prepare Ivacaftor solid dispersions in the current research study. The complexes were created by varying the molar ratios of the drug and polymer in a one-to-one ratio. Figure 1 shows a representation of the powder that was obtained.

Fig 1: Ivacaftor solid dispersions prepared by SDY technology

Solubility of Ivacaftor solid dispersions

Six formulations were created using the SDY process in conjunction with the appropriate polymer. Following the synthesis of SD utilizing the SDY technique, the resulting spray dried material was tested for solubility of the drug ingredient and the results were compared to those obtained from pure drug substance (see Figure 1). It was discovered that the formulation with (Ivacaftor: Copovidone (1:1) with sodium lauryl sulphate) ISD1 has higher solubility when compared to the pure medication (pure medication solubility is 0.001 mg/ml).

Table 3: Solubility studies of Ivacaftor solid dispersion

S. No.	Solubility of Ivacaftor Spray dried material	(mg/ml)
1	Plain drug	0.001
2	ISD1	0.22
3	ISD2	0.20
4	ISD3	0.19
5	ISD4	0.19
6	ISD5	0.18
7	ISD6	0.18

XRD Analysis

The XRD of Ivacaftor observed that multiple sharp peaks, indicating that the drug was in crystalline nature. SD Spray dried material ISD1 (Ivacaftor: Copovidone (1:1) with sodium lauryl sulfate) when exposed to X-ray beam, Observed no peaks and characteristic intensities of Ivacaftor (Figure 2). This indicates that complete conversion of crystalline Ivacaftor into amorphous form during Spray drying process. From the XRD studies, it is clearly confirmed that spray dried powder of batch no (ISD1) Drug substance converted into amorphous form (Figure 2).

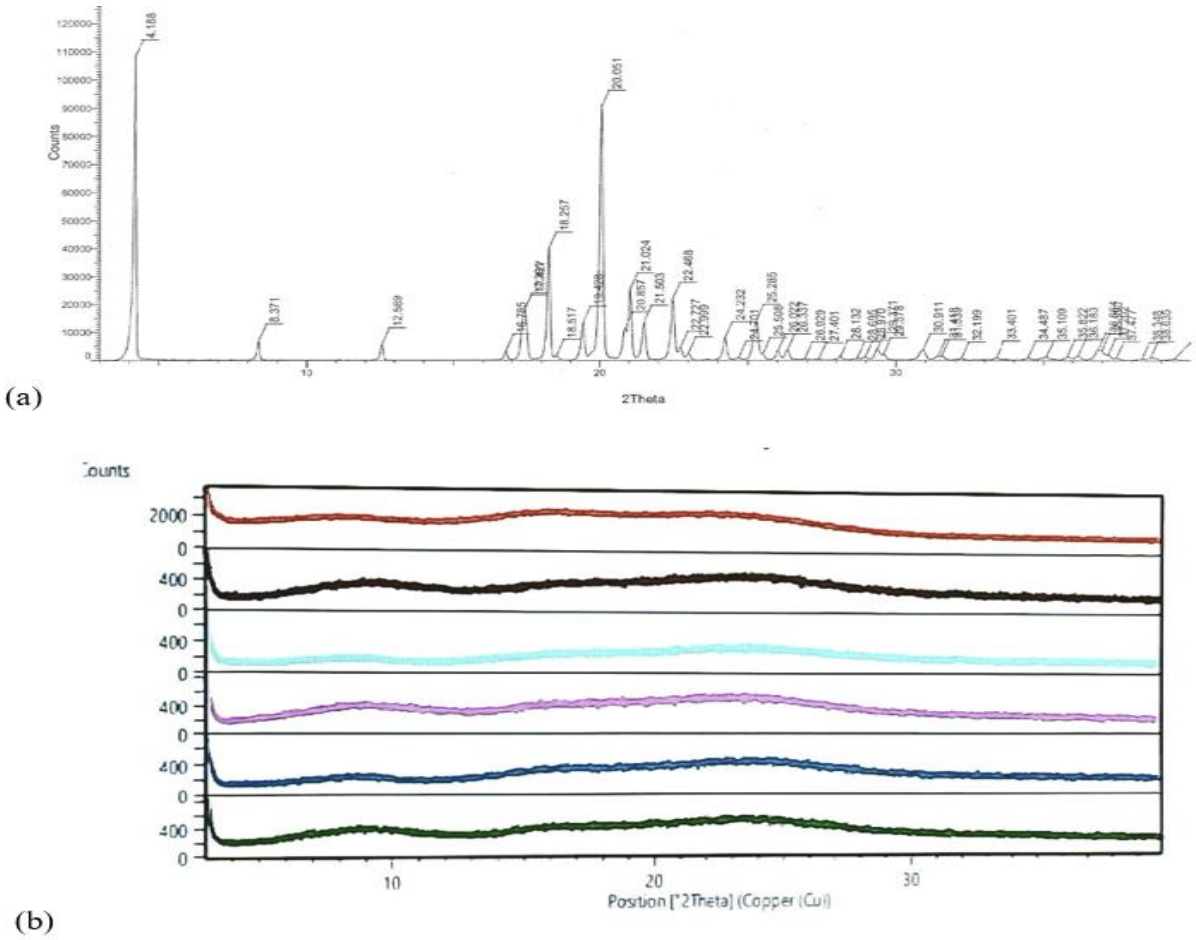


Figure 2: (a) pXRD patterns of Ivacaftor Plain drug (b) Spray dried material

DSC

Figure 6.12 depicts the DSC thermogram of Plain Ivacaftor, which shows a high peak of endothermic at 205ºC, indicating that the drug was crystalline in nature. The absence of peaks in the SD of formulation ISD1 (Ivacaftor: Copovidone (1:1) with sodium lauryl sulphate) suggests that the medication has been transformed to an amorphous form during the manufacturing process (Figure 6.13).

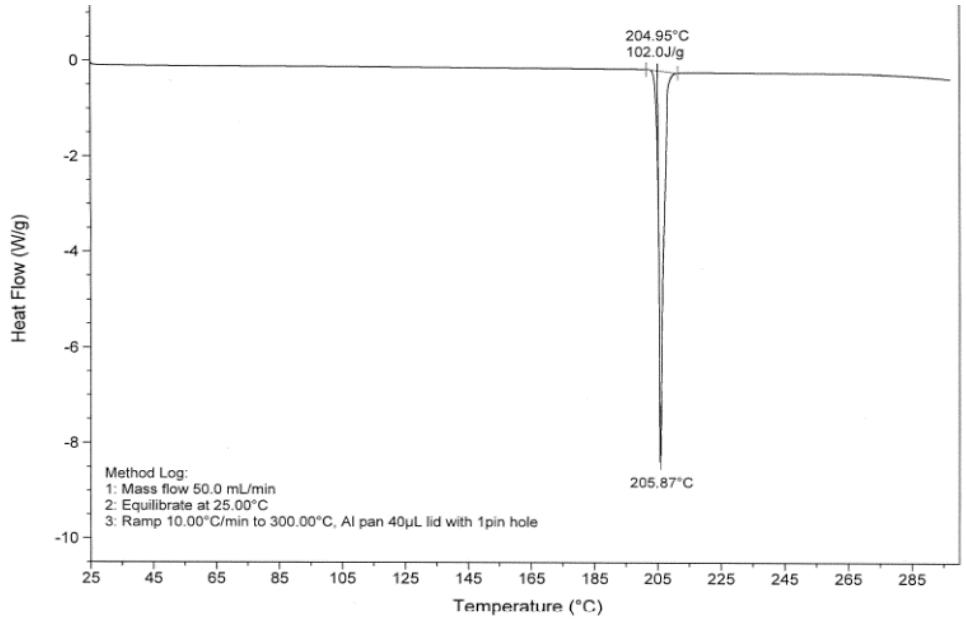


Figure 3: DSC Thermogram of Plain drug

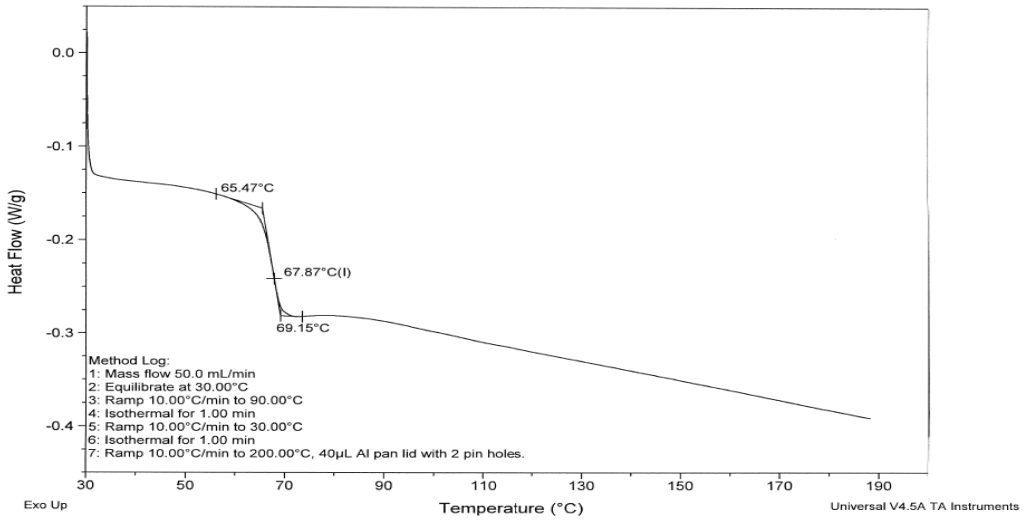


Figure 4: DSC Thermogram of Spray dried material

Physico-chemical characteristics of Ivacaftor solid dispersion tablets

It was determined that all series of tablets made were good based on their physical qualities, which included size, shape and thickness as well as Angle of repose, weight fluctuation, friability, hardness and disintegration time as well as appearance. All evaluation criteria were displayed in Figure 3, and the results demonstrated good quality, which complied with the specifications of the pharmacopoeia.

Table 6.3: Physical parameters of Spray dried Ivacaftor Tablets.

Batch Code	Weight of Tablet (mg)	Thickness (mm)	Friability test (<1%)	Hardness (KP)	Disintegration (Sec)	Angle of Repose	% Drug content
ISD1	550 ±3	6.9±0.1	0.17	7±1	45	28.2	99.5
ISD2	550 ±4	6.9±0.2	0.18	6±2	52	27.1	99.1
ISD3	550 ±5	6.9±0.2	0.16	7±1	55	28.6	98.3
ISD4	550 ±3	6.9±0.2	0.21	7±2	49	27.4	99.5
ISD5	550 ±3	6.9±0.1	0.22	6±2	59	28.2	99.9
ISD6	550 ±3	6.8±0.2	0.14	7±1	59	26.2	100.5

***In vitro* drug release studies**

Table 6.12 contains the data on drug release obtained from formulations ISD1 through ISD6 and is organized by formulation. For all formulations, the percentage of medication released is calculated. For ISD1 to ISD6, the percent of drug released after 30 minutes was 98 %, 95%, 91%, 93%, 94%, and 91%, respectively, while for the marketed formulation, the percent of drug released after 30 minutes was 90.0 % in 30 minutes.[25]. When comparing the release rate of Ivacaftor from SD to that of a plain Ivacaftor tablet, in vitro experiments have revealed an increase in the release rate of Ivacaftor from SD. Based on the in vitro drug release profiles, formulation ISD1 (Ivacaftor: Copovidone (1:1) with sodium lauryl sulphate) was shown to be the most effective formulation, with a 98.0 percent drug release rate.

Table 6.4: Dissolution profile of Ivacaftor Marketed product & SDY tablets (ISD1-ISD6).

	Mean Cumulative % drug release n= 6 units						
Time in Min	**Marketed product**	**ISD1**	**ISD2**	**ISD3**	**ISD4**	**ISD5**	**ISD6**
0	0	0	0	0	0	0	0
5	25	31	29	25	28	26	18
10	55	62	58	55	59	55	45
15	69	74	71	69	75	71	68
20	82	89	85	82	89	85	81
30	90	98	95	91	93	94	91

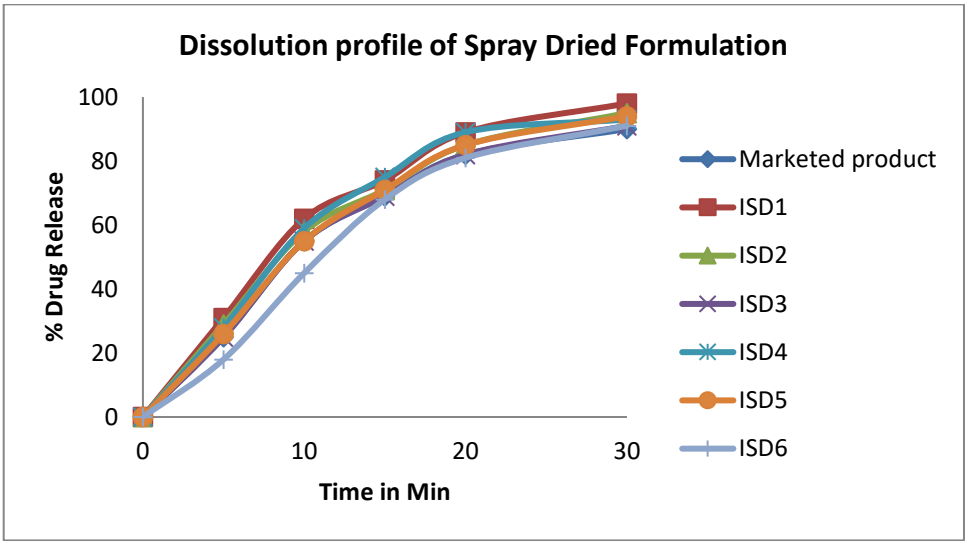


Figure 6. 15 **:** *In vitro* Dissolution profiles of Spray dried Ivacaftor Tablets

The dissolution profiles of Ivacaftor solid dispersion generated by Spray drying (ISD1) revealed that the medication was released at a somewhat higher rate at the beginning time point than at any other time point. After 30 minutes, the solid dispersion formulations developed by SDT demonstrated the maximum drug release, with 98.0 percent and 98.0 percent, respectively.

6.1.1 FT – IR studies

Observations of Ivacaftor's conspicuous peaks were made in the range of 3331 cm-1 O-H stretching. C-H stretching at 2953 cm-1 and 2988 cm-1, respectively. 1649 cm-1 N-H bending is possible. C=O stretching at a distance of 1618 cm-1. Stretching to 1286 cm-1C-N- length. ISD1 (Figure 6.22) and IHM8 (Figure 6.23) were found to have wave numbers that were closer to simple Ivacaftor when using the optimized formulations (Figure 6.21). There has been no change in the wave numbers of the optimized formulation overall. As a result, it is assumed that there is no interaction between the medicine and the excipients.

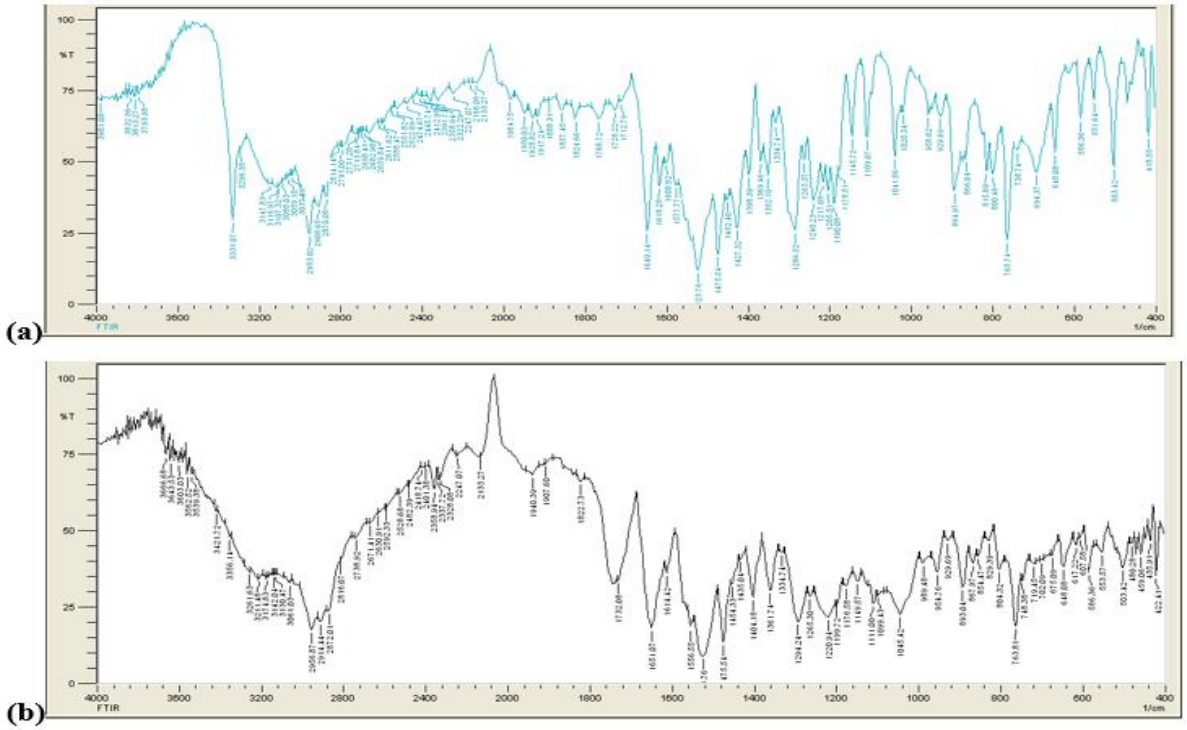


Figure: FTIR Spectra of (a) plain drug (b) Optimized formulation

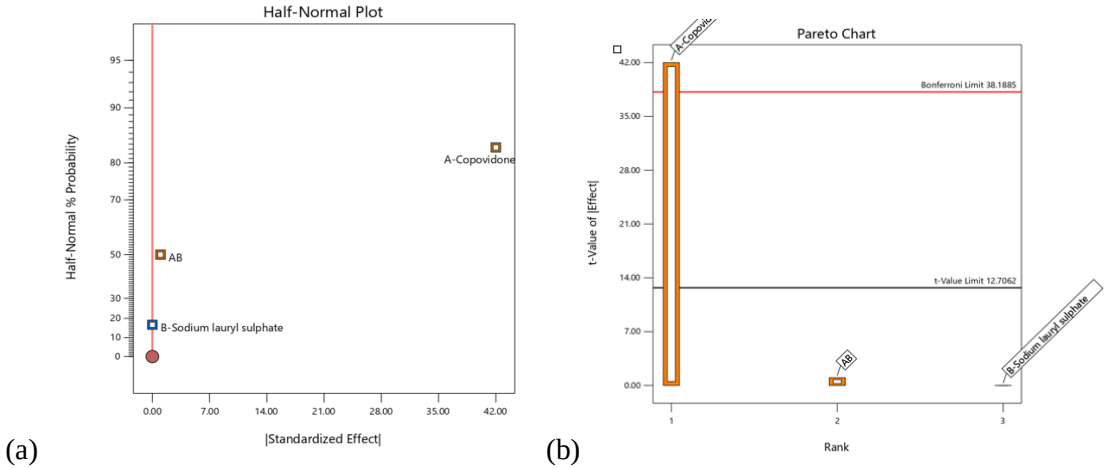
Statistical analysis

The P value of a two-factor experimental design indicates that the formulation has a statistically significant effect. An effect with a P value of less than 0.05 is considered significant; an effect with a P value of higher than 0.05 is considered non-significant. The data presented in Table 6.19 reveal that the selected model has a significant effect with a P value of 0.0103, which is less than 0.05.

Table 6.17: Experimental results for Dissolution (Y_1)

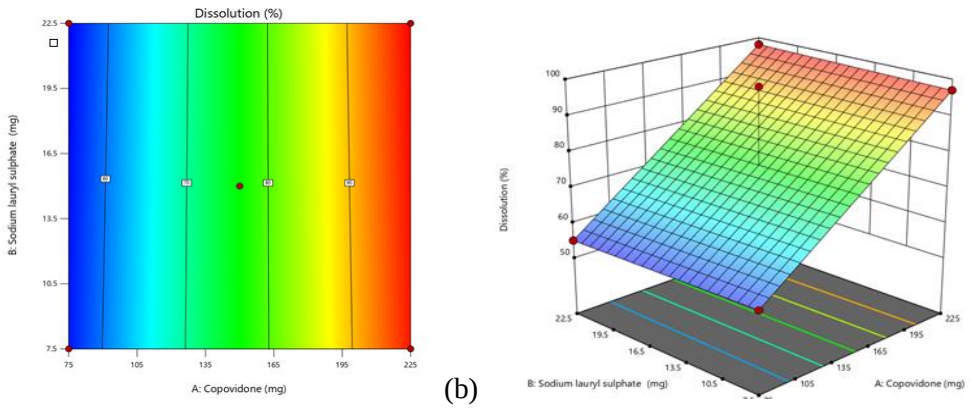
S. No.	Factors : Formulation Variables			Responses
	Batch no	A : Copovidone (in mg)	B : Sodium lauryl sulphate (in mg)	Y1 : Dissolution in 30 minutes
1	ISD7	225	22.5	98
2	ISD8	225	7.5	97
3	ISD1	150	15	98
4	ISD9	75	22.5	55
5	ISD10	75	7.5	56

According to the Half Normal Plot shown above, the formulation factors have a statistically significant effect on dissolution in 30 minutes. By doing a copovidone and sodium lauryl sulphate concentration range investigation. Copovidone exhibits the greatest effect in both the half normal plot and the pareto chat. When using the formulations, the dissolution times are within the proposed specification limit (NLT 80 percent in 30 min). As a result, for the finished formulation, 150.0 mg of soluplus per tablet and 15 mg sodium lauryl sulphate per tablet were chosen from the first formulation.



(a) (b)

Fig.:(a) Half- normal plot (b) Pareto chart



(a) (b)

Figure: (a) 2D surface plot (b) 3D-Contour plot

Figures 6.27 and 6.28 were used to investigate the interaction effects of the responses to the independent factors all at the same time. The contour plot is generated by the intersection of the Vertical axis and the Horizontal axis. Copovidone is shown by the horizontal axis, and sodium lauryl sulphate is represented by the vertical axis.

Estimation of Pharmacokinetic Parameters

On the basis of plasma concentration data, the pharmacokinetic parameters for Ivacaftor oral dosing were calculated. The data were used to compute pharmacokinetic parameters such as AUC, Cmax, and Tmax in each individual case. The data was collected using the trapezoidal rule method from the beginning of the concentration-time curve to the end of its infinity. The maximum and minimum values of Cmax and Tmax were determined from the graph. All values are reported as mean standard deviation (mean SD).

Table 7.4: *In vivo* Plasma Concentration of Ivacaftor in Rabbits (n=3)

S. No.	Time (hours)	Plasma concentration (ng/ml) (mean ± SD)	
		Reference (R): Marketed Product.	**Test (T2):**Ivacaftor immediate release Tablets 150 mg (Spray dried)
1.	1	320.3 ± 15.7	355.0 ± 16.1
2.	2	588.2 ± 28.5	591.5 ± 27.0
3.	3.5	810 ± 30.7	845.6 ± 34.2
4.	4	920 ± 27.3	931.5 ± 29.8
5.	4.5	810 ± 28.1	857.5 ± 14.6
6.	11	198.3 ± 20.1	225.1 ± 12.7
7.	18	43.6 ± 6.6	50.8 ± 5.4
8.	24	20.3 ± 4.3	22.2 ± 2.2

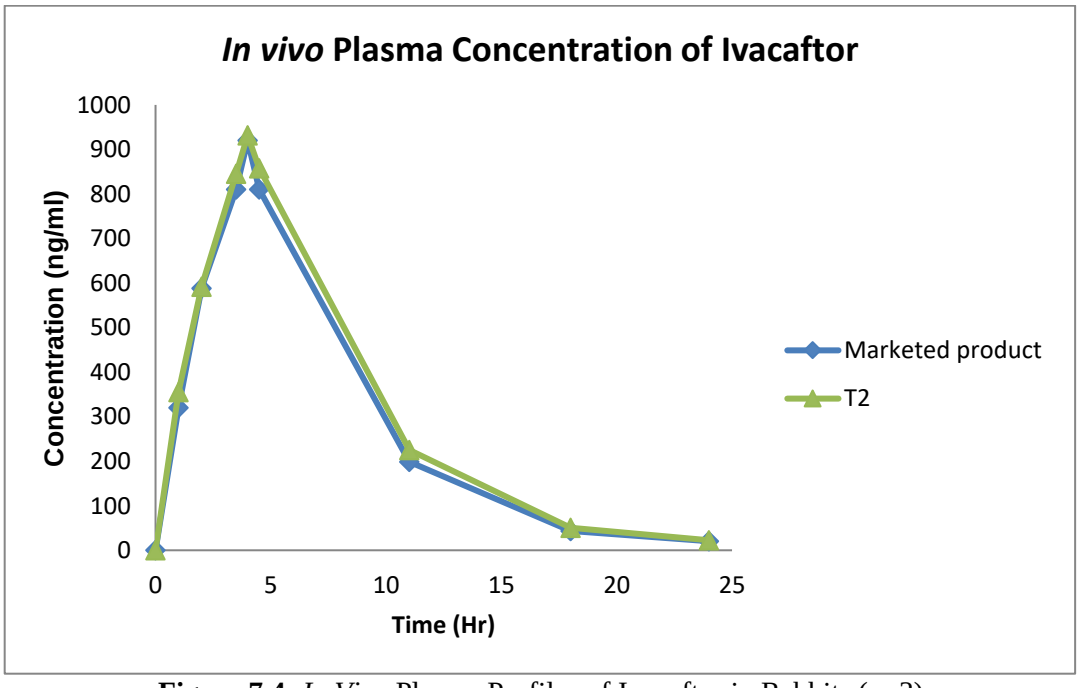


Figure 7.4: *In Vivo* Plasma Profiles of Ivacaftor in Rabbits (n=3)

A considerable increase in the dissolving rate of solid dispersions created by SDY (98 percent) in formulation ISD1 compared to plain Ivacaftor (9 percent) is observed in the in-vitro dissolution test within 30 minutes when compared to plain Ivacaftor [26]. When comparing the Ivacaftor solid

dispersion technique and Spray drying, the release of the drug was slightly higher at the first time points when comparing the two techniques. The drug release was observed to be 9 percent in the unflavored medication. In the order solid dispersions of SDY> Plain drug material, Ivacaftor shows an increase in the rate of dissolution of the drug[27].

Describes the mechanism by which drug substance is solubilized and better wetting is achieved by the use of hydrophilic carriers rich in microenvironment, which are generated at the surface of drug substance crystals following the dissolution rate. Using polymers in the solid dispersion approach, the crystallinity of the medicinal material was lowered, which was beneficial. The results of DSC and XRD analysis revealed that the crystal structure of Ivacaftor was being converted to an amorphous state. Finally, it was determined that solid dispersion of Ivacaftor utilizing hydrophilic polymers SDY would improve the water dissolution rate, solubility, and systemic availability of the drug. Design Expert 11 software was used to determine whether or not excipients had a statistically significant effect. The findings of the DOE performed on soluplus and sodium lauryl sulphate demonstrate that the use of soluplus has a statistically significant effect on the outcomes of the Half normal chart and the Perito chart. During the in vivo evaluation of Ivacaftor, it was discovered that the plain drug, spray dried material, and hot melt extraction material had a substantial impact. In vivo examination of both ISD1 and plain drug was performed. According to the results, the Cmax of Plain drug, ISD1 and ISD2 were found to be 104.10 4.1 mg/ml, 972.57 29.1 mg/ml, and 931.50 29.8 mg/ml (respectively).

Conclusion

Using a simple and scalable spray drying process, we were able to produce ivacaftor SD tablet compositions that were previously unheard of. Ivacaftor tablets are made with the carriers Copovidone, Hypromellose 5cps, and Soluplus, as well as several sodium lauryl sulphate surfactants. The SEM, XRD, DSC, FTIR, drug content, solubility, and dissolution of Ivacaftor tablets were used to characterize the tablet formulation. In this way, spray-dried solid dispersions have the potential to be an effective approach of increasing the bioavailability of ivacaftor in humans.

Acknowledgement

The authors were thankful to management of hetero labs for providing facilities to carry out the research work,

References

1. B.R. Giri, J. Kwon, A.Q. Vo, A.M. Bhagurkar, S. Bandari, D.W. Kim, Hot-Melt Extruded Amorphous Solid Dispersion for Solubility , Stability , and Bioavailability Enhancement of Telmisartan, (2021) 1–18.
2. P.R. Guntaka, S. Lankalapalli, SOLUBILITY AND DISSOLUTION ENHANCEMENT OF IVACAFTOR TABLETS BY USING SOLID DISPERSION TECHNIQUE OF HOT-MELT EXTRUSION - A DESIGN OF EXPERIMENTAL APPROACH, 12 (2019).
3. A.A. Ambike, K.R. Mahadik, A. Paradkar, Spray-Dried Amorphous Solid Dispersions of Simvastatin , a Low T g Drug : In Vitro and in Vivo Evaluations, 22 (2005) 990–998. https://doi.org/10.1007/s11095-005-4594-z.
4. A. Nair, D. Khunt, M. Misra, Application of quality by design for optimization of spray drying process used in drying of Risperidone nanosuspension, Powder Technol. (2018) #pagerange#. https://doi. org/ 10.1016/ j. powtec. 2018.09.096.
5. J. Chen, M.U. Ahmed, C. Zhu, S. Yu, W. Pan, T. Velkov, J. Li, Q. Tony, In vitro evaluation of drug delivery behavior for inhalable amorphous nanoparticle formula- tions in a human lung epithelial cell model, Int. J. Pharm. 596 (2021) 120211. https://doi. org/10.1016/j.ijpharm.2021.120211.
6. M. Davis, G. Walker, Recent strategies in spray drying for the enhanced bioavailability of poorly water-soluble drugs, J. Control. Release. 269 (2018) 110–127. https://doi.org/ 10.1016/j.jconrel.2017.11.005.
7. P.R. Guntaka, S. Lankalapalli, SOLID DISPERSION - A NOVEL APPROACH FOR BIOAVAILABILITY ENHANCEME-
8. NT OF POORLY WATER-SOLUBLE DRUGS IN SOLID ORAL DOSAGE FORMS, 12 (2019).
9. V. Mishra, S. Thakur, A. Patil, A. Shukla, ce pt cr t, Expert Opin. Drug Deliv. 0 (2018) 1. https://doi.org/10.1080/17425247.2018.1504 768.
10. P.K. Desu, V. Pasam, V. Kotra, Implications of superporous hydrogel composites-based gastroretentive drug delivery systems with improved biopharmaceutical performance of fluvastatin, J. Drug Deliv. Sci. Technol. 57 (2020) 101668. https://doi.org/10.1016/ j. jddst. 2020.101668.
11. G. Soni, K.S. Yadav, M.K. Gupta, Journal of Drug Delivery Science and Technology QbD based approach for formulation development of spray dried microparticles of erlotinib

hydrochloride for sustained release, J. Drug Deliv. Sci. Technol. 57 (2020) 101684. https://doi.org/ 10.1016/ j.jddst. 2020. 101684.
12. P. Chandra, R. Guntaka, A. Pradesh, A COMPARATIVE STUDY OF LEDIPAS-VIR SOLID DISPERSION TECHNIQUE USING, 9 (2018) 5145–5154. https://doi. org/ 10. 13040/IJPSR.0975-8232.9(12).5145-54.
13. P. Chandra, R. Guntaka, DESIGN AND DEVELOPMENT OF SPRAY DRIED TELAPREVIR FOR IMPROVING THE DISSOLUTION FROM TABLETS Purna Chandra Reddy Guntaka * and Srinivas Lankalapalli, 7 (2017) 430–438.
14. A. Ouranidis, N. Gkampelis, E. Vardaka, A. Karagianni, D. Tsiptsios, I. Nikolakakis, K. Kachrimanis, Overcoming the Solubility Barrier of Ibuprofen by the Rational Process Design of a Nanocrystal Formulation, (2020).
15. X. Zhang, J. Zhao, J. Guan, X. Zhang, L. Li, S. Mao, AC SC, J. Drug Deliv. Sci. Technol. (2019). https://doi.org/10. 1016/j.jddst. 2019. 01.018.
16. N. Al-zoubi, F. Odah, W. Obeidat, A. Al-jaberi, I. Partheniadis, I. Nikolakakis, Department of Pharmaceutics and Pharmaceutical Technology, J. Pharm. Sci. (2018). https://doi.org/ 10.1016/ j.xphs. 2018. 04.028.
17. S. Ankur, K. Vaishali, P. Santosh, Lornoxicam Immediate Release Tablet Using Spray-Dried Cellulose Lornoxicam Imme- diate Release Tablet Using Spray-Dried Cellulose Nanofibers (NFC) as Novel Tablet Excipient, (2016).
18. P.N. Remya, T.S. Saraswathi, S. Sangeetha, N. Damodharan, R. Kavitha, Formulation and Evaluation of Immediate Release Tablets of Acyclovir, 8 (2016) 1258–1261.
19. I. Amlodipine, tablet using response surface methodology, (2011). https://doi.org/ 10. 4103/0973-8398.80069.
20. S.B. Jadhav, S.H. Rajeghadage, R.S. Bathe, Formulation and evaluation of immediate release tablets of Imipramine hydrochloride Formulation and evaluation of immediate release tablets of Imipramine hydrochloride, (2014). https://doi.org/10.7439/ijbar.
21. I. Release, Kulkarni and Bahera, 6 (2015) 808–815. https://doi.org/ 10.13040/ IJPSR. 0975-8232.6(2).808-15.
22. M.S.V. Sakuntala, A.L. Rao, M.W. Carey, M. Satya Venkata Sakuntala 1 , A. Laksh- mana Rao 2 , M. William Carey 3, 45 (2021) 451–460.
23. H. João, M. Jorge, D. Slavomíra, Ac ce pt cr, Pharm. Dev. Technol. 0 (2020) 000. https:// doi.org/ 10.1080/10837450.2020.1863985.
24. D. Law, E.A. Schmitt, K.C. Marsh, E.A. Everitt, W. Wang, J.J. Fort, S.L. Krill, Y. Qiu, Ritonavir – PEG 8000 Amorphous Solid Dispersions : In Vitro and In Vivo Evaluations, 93 (2004) 563–570.
25. N. Zerrouk, C. Chemtob, P. Arnaud, S. Toscani, In vitro and in vivo evaluation of carbamazepine-PEG 6000 solid dispersions, 225 (2001) 49–62.
26. I. Pharmacy, compressed solid dispersions and freeze dried sildenafil citrate sublingual tablets for management of pulmonary arterial hypertension, 62 (2012) 411–432. https://doi.org/10.2478/v10007-012-0027-9.
27. Y.A.N. He, C. Ho, Amorphous Solid Dispersions : Utilization and Challenges in Drug, J. Pharm. Sci. 104 (2015) 3237–3258. https://doi.org/10.1002/jps.24541.
28. M. Newa, K. Hari, D. Xun, T. Kwon, J. Ae, B. Kyu, J. Soo, W. Seok, C. Soon, H. Gon, Preparation , characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188, 343 (2007) 228–237. https:// doi.org/ 10.1016/ j.ijpharm. 2007.05.031.
29. Ravi Kumar K, Pavan Kumar K Formulation and evaluation of Taste masking Lercandipine hydrochloride Oral Disinte-grating Tablets Int. J. Res. Pharm. Sci., 2021, 12(2), 1055-1062.
30. Kota RK, Gande S. Development and Evaluation of Olmesartan medoxomil Controlled release floating microspheres using natural gums. International Journal of Pharmaceutical Sciences and Nanotec-hnology (IJPSN). 2017 Jul 31;10 (4):3788-94.
31. Kota RK, Bhikshapathi DV, Gande S. Formulation and In vivo Evaluation of Mucoadhesiv Microspheres of Valsartan using Natural Gum. International Journal of Pharmaceutical Sciences and Nanotechno-logy (IJPSN). 2019 Jan 31;12(1):4393-402.