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Review Article

FORMULATION AND INVITRO CHARACTERIZATION OF IVACAFTOR SOLID DISPERSION BY SOLID SOLVENT EVAPORATION TECHNIQUE

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ABSTRACT

Ivacaftor is a cystic fibrosis transmembrane conductance regulator. It is used for the treatment of osteoarthritis. It is an BCS class-II drug having 12-14 hours half-life. Solid dispersions of Ivacaftor were prepared with different carriers in different ratios of drug and carrier (1:1,1:2&1:3) By using Mannitol, Crospovodine, and Sodium Starch Glycolate. Results of prepared solid dispersions of Ivacaftor by solvent evaporation method were discussed which includes solubility, melting point determination, drug content uniformity, entrapment efficiency and invitro dissolution studies. Characterization in solid state was done by various analytical techniques such as FT-IR studies. Finally by comparing all the formulations, formulation (F6) containing Ivacaftor + Crospovidone (1:3) shows better results by solvent evaporation method at the end of 60 min with maximum drug release of 99.48, hence it was selected as the best formulation. The optimized formulation follows zero order release kinetics.

Keywords: Ivacaftor, Crospovidone, Manitol, SSG & FTIR.

INTRODUCTION

Common techniques for improving the solubility & absorption of inadequately water-soluble drugs include micronization, the use of surfactants, and the production of solid dispersions.[1] Chiou & Riegelman [2] Simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous phases, and compound or complex formation are the six types of drug-carrier interactions that can occur in solid-state dispersions. Recently, the use of solid dispersions on medications with low water solubility has been the subject of much research to improve solubility.[3, 4, 5, 6, 7, & 8.] Due to poor solubility behaviour, the bioavailability of a medicinal substance may be restricted. Previous studies [9] have found that the bioavailability and dissolving rate of a solid dispersion were increased when the medication was liberated from its delivery mechanism as a tiny or colloidal particle. However, recent study suggests that the rate-limiting process in a hydrophobic micro emulsion solution is agglomeration..[10] The benefits of a sound dispersion method are in conflict with this discovery. Early research in our lab revealed a substantial function for the carrier in this compromising impact. [11]. The benefits of a sound dispersion method are in conflict with this discovery. Early research in our lab revealed a substantial function for a carrier in this compromising impact.[12]

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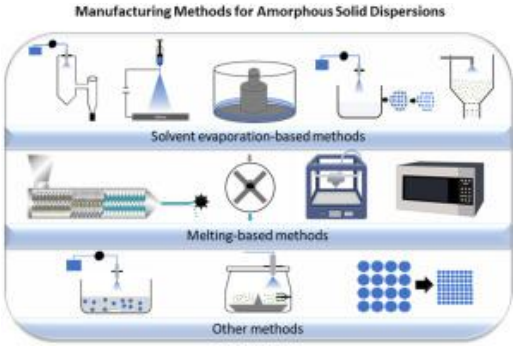

Figure.No.1 Solid dispersion technique

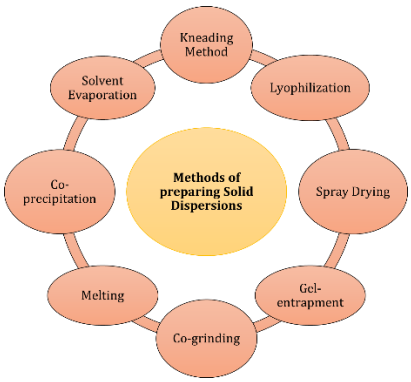

Figure.No.2 Solid Dispersion Techniques[4]

It is preferable to utilise a polymer with a high glass transition temperature since it enables the formation of the crucial glassy state. Additionally, if a solid dispersion's transition temperature is greater than the drug's, it can prevent intermolecular interactions from occurring at room temperature during storage, further lowering the likelihood of nucleation & crystal formation.[13, 14.]

Vertex Pharmaceuticals produces and distributes it. On January 31, 201213, the Food and Drug Administration granted its approval, and Health Canada later that year. For the treatment of CF, ivacaftor is given both as a monotherapy and in combination with other medications.1The Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein, an ion channel involved in the transport of chloride and sodium ions across cell membranes, is the gene responsible for the autosomal recessive condition known as cystic fibrosis. Epithelial cells in organs such the lungs, pancreas, liver, digestive system, and reproductive tract are where CFTR is active.

Changes in the CFTR gene affect the protein's synthesis, function, or folding, which leads to improper fluid and ion transport across cell membranes. In turn, this makes CF patients more prone to problems including infections, lung damage, pancreatic insufficiency, and malnutrition by clogging the ducts of the organs where it is generated.[15]

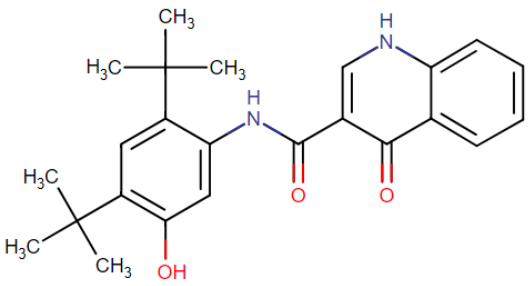

Figure.No.3 Structure of Ivacaftor

Prior to the creation of ivacaftor, treatments for CF were mostly focused on symptom management, mucus clearance, nutrition support, and infection control rather than advances in the underlying disease process or lung function (FEV1). It is noteworthy that ivacaftor was the first drug authorized for treating the fundamental causes of cystic fibrosis (CF) (abnormalities in CFTR protein activity) rather than only treating symptoms.

MATERIALS AND METHODOLOGY:

Ivacaftor API was procured from B.M.R Chemicals, Hyderabad and Mannitol, Cross Povidone, Methanol, PEG 4000 CCS, were procured from S.D Fine Chemicals.

PREPARATION OF SOLID DISPERSIONS OF IVACAFTOR:

There are several carriers, which have been reported for the preparation of solid dispersions by using Mannitol, Cross povidone and SSG various methods of preparation.

a. Solvent evaporation

In solvent evaporation method, the drug and carriers weremixedin1:1,1:2 and 1:3 ratios in methanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverized and passed throughsieve#60. And now the obtained product was collected.

Table.No.1 Formulation of Solid Dispersions of Ivacaftor

Formulation code	**Drug: polymer ratio (ivacaftor: Mannitol)**
F1	1:1
F2	1:2
F3	1:3
Formulation code	**Drug: polymer ratio (ivacaftor: Crospovidone)**
F4	1:1
F5	1:2
F6	1:3
Formulation code	**Drug: polymer ratio (ivacaftor: SSG)**
F7	1:1
F8	1:2
F9	1:3

Evaluation of Solid Dispersions:

Prepared polymer drug conjugates were evaluated by

- Estimation of drug content
- Entrapment efficacy
- *In- vitro* dissolution studies
- In vitro Release kinetics

IN VITRO DISSOLUTION STUDY:

The generated solid dispersions were put in a capsule with 5 mg of Ivacaftor weight equivalent and were then subjected to in vitro disintegration. USP type 2 paddle methods were used in the dissolution test (apparatus II). 6.8 pH buffer was employed as the dissolution media, and the dissolution medium was maintained at 37 0.5 o C. The stirring speed was 50 rpm. 5 ml samples were taken out at regular intervals, filtered, and replaced with 5 ml of fresh dissolution medium. Dilutions were made as needed, and the samples were then tested for the presence of Ivacaftor at 255 nm using a UV-visible spectrophotometer.

KINETICS OF DRUG RELEASE:

The mechanism of drug release for the Ivacaftor solid dispersions was determined using zero order and first order.

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.

PRCORMULATION STUDIES

a) Solubility studies: Solubility of Ivacaftor was carried out in different buffers. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 hrs at 25°C under constant vibration.

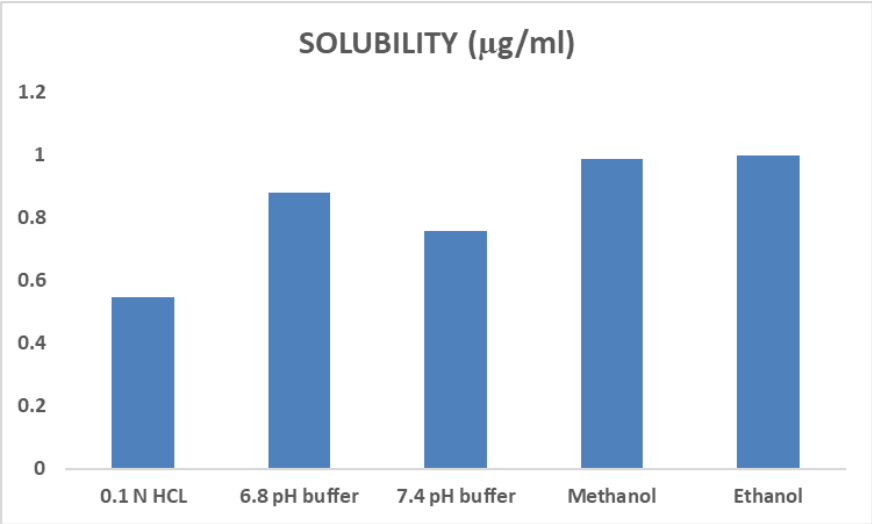

Figure.No.4 Solubility studies of Ivacaftor

Discussion:
From the above conducted solubility studies in various buffers we can say that 6.8 pH buffer solution has more solubility when compared to other buffer solutions.

UV Scan Spectrum of Ivacaftor: UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution. Instrument which measure the ratio, or function of ratio, of the intensity of two beams of light in the U.V-Visible region are called Ultraviolet-Visible spectrophotometers

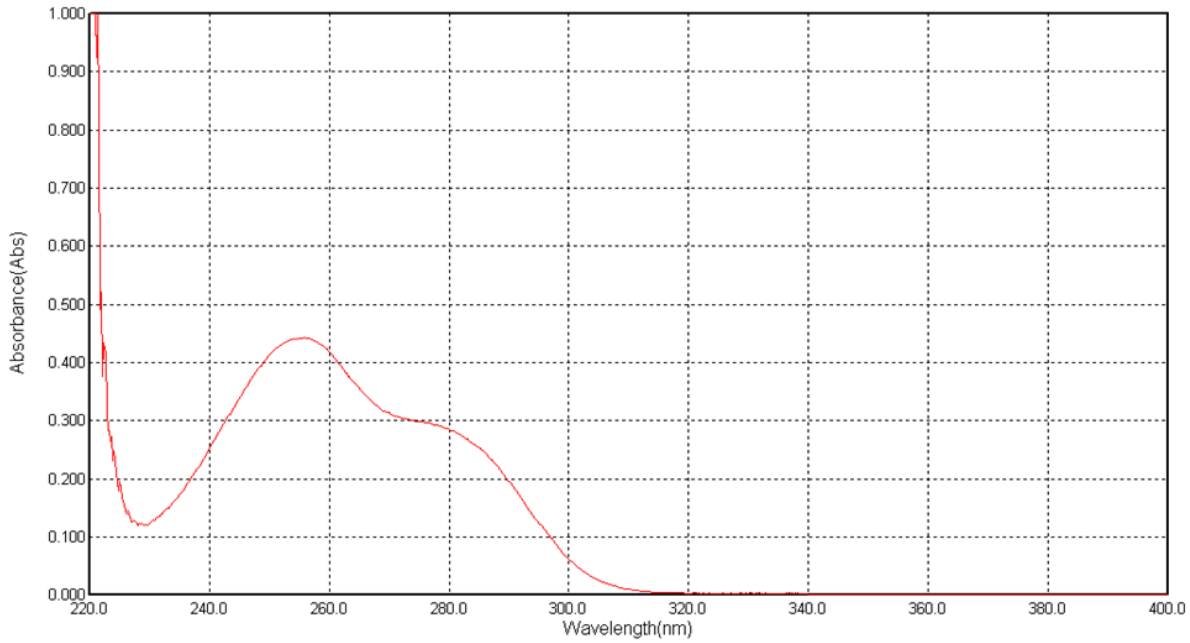

Figure.No.5 Uv Spectrum of Ivacaftor

Discussion: Ivacaftor at 10µg/ml was found to be 255nm.

Calibration curve data of Ivacaftor: 10mg of Ivacaftor was taken in a10ml volumetric flask. To The solution was made up to the mark with 6.8pH buffer to give 1000 µg /ml concentration. From this Solution 1ml is diluted to10mlwith,6.8pH buffer to give 100 µg

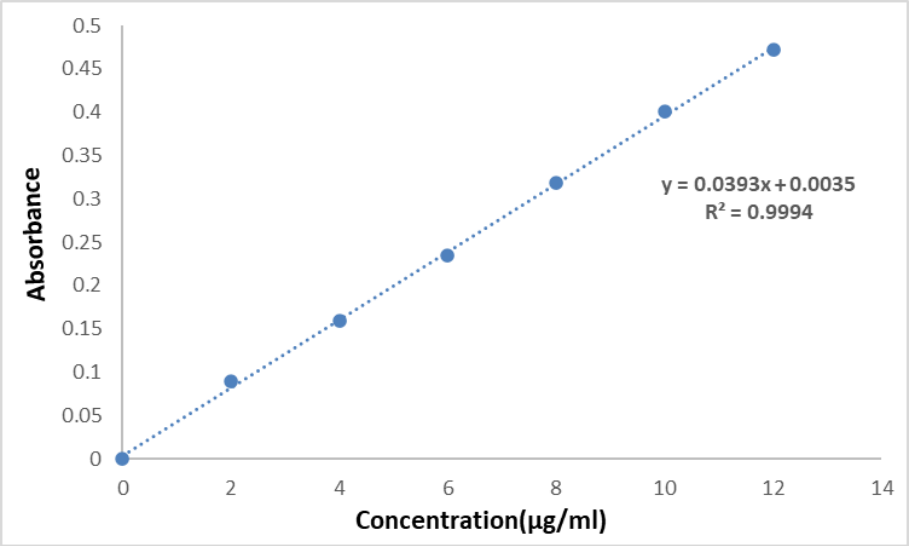

Figure.No.6 Calibration curve

Discussion: The linearity was found to be in the range of 2-12µg/ml in pH 6.8 buffer. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

Drug excipient compatibility:

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

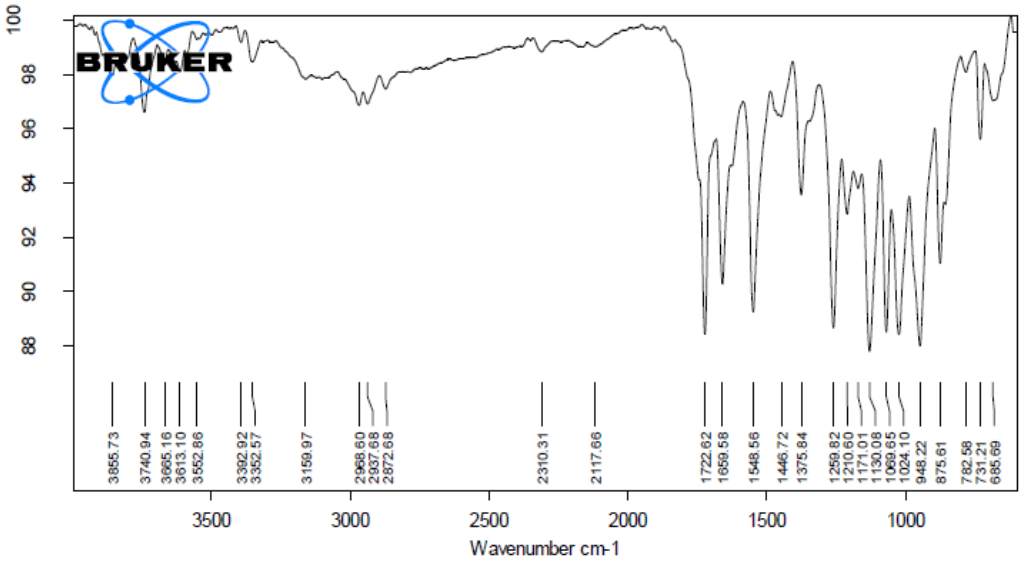

Figure.No.7 IR spectrum of pure Ivacaftor

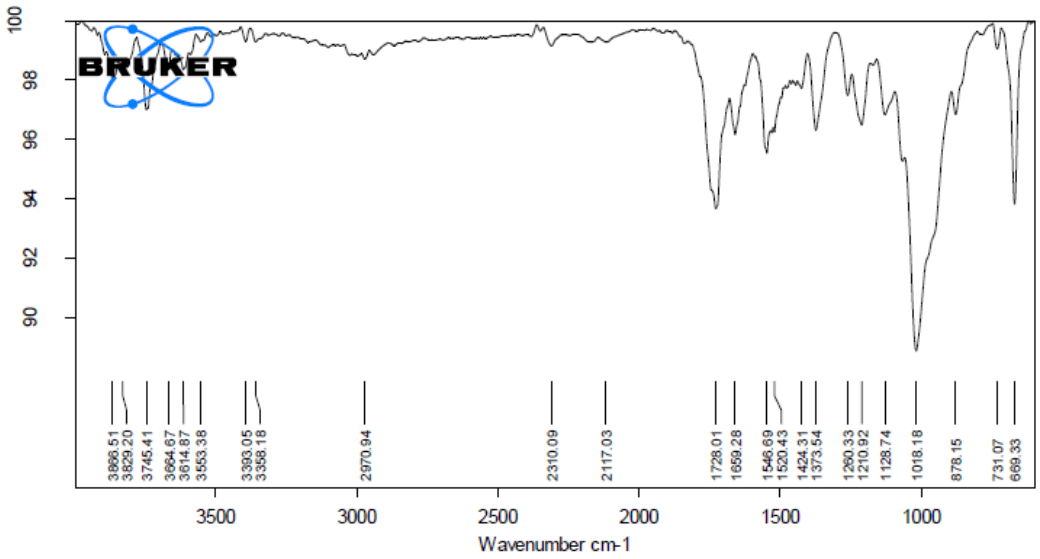

Figure.No.8 IR spectrum of Ivacaftor Optimized Formulation

Discussion: From the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Ivacaftor) and optimized formulation (Ivacaftor : excipients) which indicates there are no physical changes.

Percentage drug content of solid dispersions

Table.No.2 Percentage drug content of solid dispersions

Formulation code	Drug Content
F1	93.42
F2	91.23
F3	90.64
F4	93.30
F5	95.15
F6	97.66
F7	95.52
F8	92.17
F9	90.89

Discussion: The percentage Drug content of the formulated solid dispersions was found to be in the range of 90.64- 97.% respectively.

Entrapment efficacy: -

Table.No.3 Entrapment efficiency of solid dispersions by solvent evaporation method

Formulation code	Entrapment efficiency
F1	95.25±0.67
F2	93.54±0.71
F3	92.30±0.11
F4	95.96±0.39
F5	96.22±0.42
F6	98.78±0.50
F7	96.53±0.63
F8	94.88±0.77
F9	93.62±0.18

Discussion: The entrapment efficacy of the formulated solid dispersions by solvent evaporation method was found to be in the range of 92.30±0.10-98.78±0.50 respectively.

INVITRO DRUG RELEASE STUDIES OF SOLID DISPERSIONS:

Table.No.4 *Invitro* drug release studies for formulations (F1-F9)

Time (Min)	Percentage drug release								
	Ivacaftor : Mannitol			Ivacaftor : Cross povidone			Ivacaftor : SSG		
	1:1 (F1)	1:2(F2)	1:3 (F3)	1:1 (F4)	1:2 (F5)	1:3(F6)	1:1(F7)	1:2(F8)	1:3(F9)
0	0	0	0	0	0	0	0	0	0
5	59.78	42.66	51.78	42.35	35.24	**57.58**	42.75	35.26	35.23
10	67.35	56.67	65.35	52.69	42.75	**64.25**	53.12	45.93	47.55
15	74.75	64.57	71.75	61.78	53.35	**70.69**	67.65	56.71	56.79
30	80.95	75.52	77.95	68.25	62.69	**76.28**	72.78	61.52	65.52
45	8.35	84.98	86.35	76.35	74.78	**87.26**	81.34	76.78	73.78
60	92.12	94.84	97.12	89.78	88.78	**99.48**	89.86	92.28	96.64

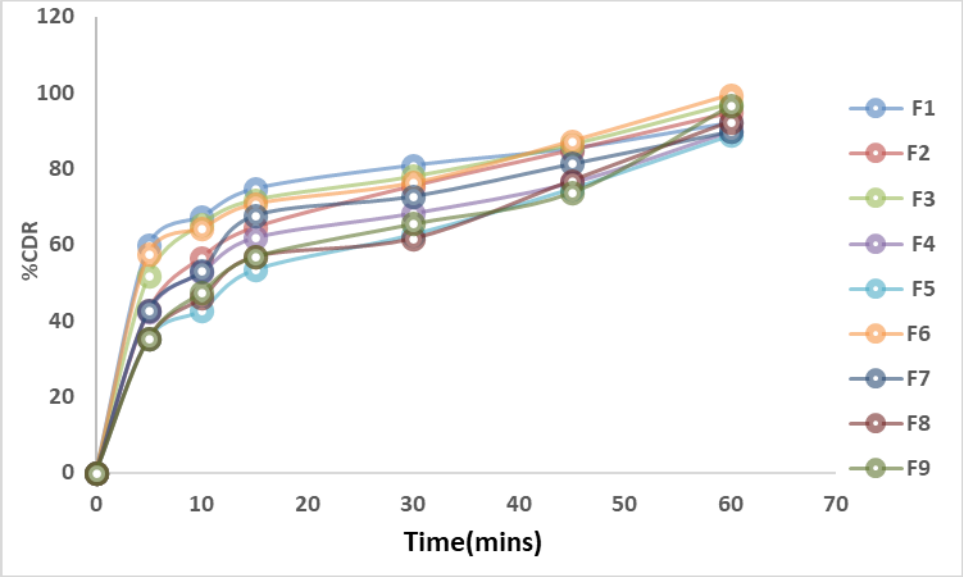

Figure.9. *Invitro* drug release studies

Discussion: In-vitro drug release of Ivacaftor solid dispersions with Mannitol in various ratios were observed which shows at the end of 60 mins, the formulation F1 releases 92.12%, formulation F2 releases 94.84%, F3 releases 97.12%, while Cros povidone used as carrier shows formulation F4 releases 89.78%, formulation F5 releases 88.78%, and formulation F6 releases 99.48%, while SSG used as carrier shows formulation F7 releases 89.86%, formulation F8 releases 92.28%, and formulation F9 releases 96.64%.Among all formulation F3 formulation shows maximum drug release at the end of 60minutes so it was chosen as optimized formulation.

IN-VITRO DRUG RELEASE KINETICS STUDIES FOR BEST FORMULATION F6:

Zero order release kinetics studies:

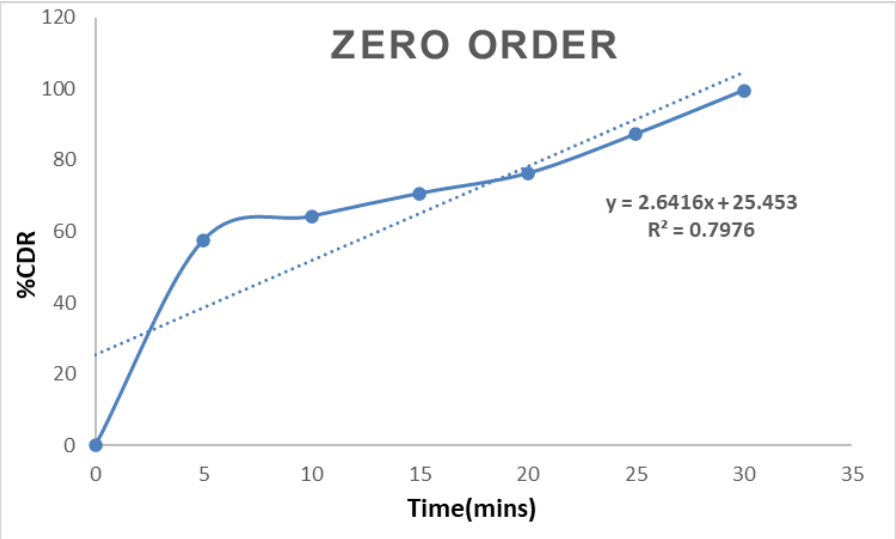

Figure. .Zero order release profile for best formulation (F6)

First order release kinetics studies:

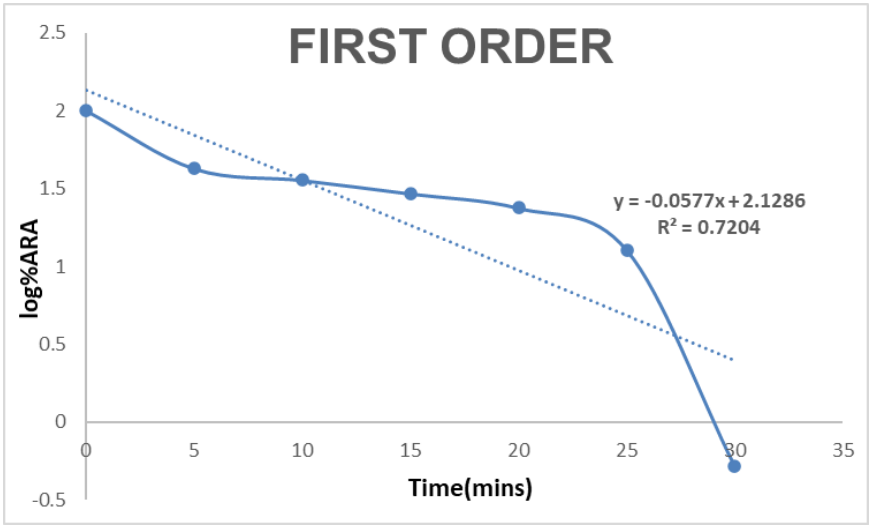

Figure. First order release profile for best formulation (F6)

Table.No.5 order of kinetic values of Formulation F6

Order of kinetics	Zero Order	First Order
Regression values	0.797	0.720

Discussion:

The drug release from the tablets was explained by using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation F6 follows Zero order kinetics.

SUMMARY:

The ability of a pharmaceutical treatment intended for oral administration to treat a condition depends on how well it is absorbed by the digestive system. It is generally known that the rate-limiting stage in the gastro intestinal absorption of a medicine from a solid dose form is frequently disintegration. Pharmaceuticals that are poorly soluble have been shown to be unpredictable and slow to be absorbed when compared to drugs that are more soluble. As a result, these medications pose significant obstacles to the creation of bioavailable dosage forms. Therefore, it is necessary to enhance the water solubility, rate of dissolution, and bioavailability of these drugs from their oral solid dosage forms. To improve the dissolving properties and bioavailability of medications that are only weakly water-soluble, mannitol and cross-povidone have been used as a solid dispersion method. This work has demonstrated how a solid dispersion method can considerably improve the Ivacaftor 's capacity to dissolve. Ivacaftor is cystic fibrosis transmembrane conductance regulator (CFTR). Following an EU-wide review of Ivacaftor, its use has been restricted in order to minimise the risks of cystic fibrosis. Therefore, an effective formulation that can increase the solubility and dissolution rate of this model medicine may be useful. In order to increase the solubility and, consequently, the dissolving rate, efficiency, and bioavailability of the weakly soluble medication Ivacaftor , investigations were conducted using the solid-dispersion technique using mannitol, Crospovidone, and SSG. The introduction section provided a succinct explanation of solid dispersions. In addition, in the chapter's introduction, numerous methods for improving

solubility, particularly solid dispersion technology, were covered. The aim and objective was also discussed. Ivacaftor 's entire pharmacological profile and excipient profiles included information on their use, contraindications, and side effects. literature review of prior preparation and research on solid dispersions using a variety of medications and techniques. In-depth explanations of the methodology, materials used, and experimental techniques used in this study were provided. It was further taught how to make physical mixes and solid Ivacaftor dispersions via solvent evaporation and how all of the assessment parameters work. Ivacaftor solid dispersions were created using several carriers in varying drug and carrier ratios (1:1, 1:2 and1:3). Results of Ivacaftor solid dispersions made using the solvent evaporation method, including solubility, melting point estimation, drug content homogeneity, entrapment efficiency, and in vitro dissolution experiments, were discussed. Numerous analytical methods, including FT-IR studies, were used for solid-state characterization. The formulation **(F6)** combining Ivacaftor + Crospovidone (1:3) showed better results by solvent evaporation method at the end of 60 min with drug release of 99.48%, hence it was chosen as the best formulation after comparing all the formulations (F1-F9).

CONCLUSION:

By using the solvent evaporation method, solid dispersions were prepared using cross povidone and mannitol. By examining the Ivacaftor with Crospovidone dissolution studies (1:3). indicates improved medication release. Additionally, all of the created solid dispersions underwent evaluation, with the results detailed in the preceding information.The following conclusions were drawn from the present investigations. From the Solubility studies in various buffers we can say that 6.8 pH buffer has more solubility when compared to other buffer solutions for Ivacaftor . Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (drug + excipients) which indicates there are no physical changes. All the formulations of Ivacaftor were prepared solvent evaporation method All the prepared solid dispersions were evaluated for drug content and entrapment efficiency. The invitro dissolution studies of Ivacaftor was performed.

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