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ENHANCEMENT OF DISSOLUTION AND BIOAVAILABILITY OF EZETIMIBE BY SPRAY DRIED MICROPARTICLES USING HP- β - CYCLODEXTRIN POLYMER

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ABSTRACT: Objective: Enhancement of oral bioavailability of poorly water soluble drugs is the most challenging aspects of drug development. It is very important to find appropriate formulation approaches to improve the aqueous solubility and bioavailability of poorly aqueous soluble drugs. Ezetimibe is a new lipid lowering agent in the management of hypercholesterolemia. The drug is water-insoluble, lipophilic, and highly permeable. Therefore, bioavailability of ezetimibe may be improved by increasing its solubility. **Method:** The aim of the present study was to improve the solubility and dissolution rate of Ezetimibe by preparing microspheres by spray drying technique using HP β -cyclodextrin. Ezetimibe microspheres containing different ratios of HP- β -cyclodextrin were produced by using Propanol and water (50:50) as a solvent system. The prepared formulations containing different ratios of Ezetimibe and HP β -cyclodextrin were evaluated for solubility and *in-vitro* dissolution. The prepared formulations were characterized by differential scanning calorimetry (DSC), X-ray diffraction spectroscopy (XRD), fourier transform infra-red spectroscopy (FTIR) and scanning electron microscopy (SEM). Dissolution profile of the prepared spray dried microspheres was compared with its physical mixture and pure sample. **Result:** Spray dried microspheres exhibited decreased crystallinity. The solubility of microspheres containing Ezetimibe and HP- β -cyclodextrin (1:3w/w) exhibited tenfold increases and dissolution of same ratio microsphere showed 99% release in 20 min while same composition in physical mixture showed 37% release in 20 min. Consequently, from the above result it can be concluded that spray dried microspheres of Ezetimibe is a useful technique to improve the solubility and dissolution of poor water soluble drug like Ezetimibe.

INTRODUCTION: Ezetimibe, a poorly water soluble drug and the oral delivery of drug is frequently associated with low bioavailability. It is used as an anti-hyperlipidaemia drug in the management of: hypercholesterolemia, homozygous sitosterolemia (phytosterolemia).

After oral administration, drug molecule is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (drug molecule-glucuronide)¹⁻³. Rate of absorption and extent of bioavailability for such insoluble hydrophobic drug are controlled by rate of dissolution in gastro-intestinal fluids. However, its oral bioavailability is very low, probably due to poor solubility in water and insufficient dissolution rate. Consideration of the modified Noyes-Whitney equation provides some hints about the dissolution rate of poorly soluble compounds might be improved to minimize the limitations to their oral

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availability. There have been numerous efforts to improve drug dissolution rates. These include (a) reducing the particle size to increase the surface area; (b) using water-soluble carriers to form inclusion complexes; (c) solubilization in surfactant systems; (d) using pro drugs and drug derivatization; and (e) manipulation of the solid state of drug substances to improve the drug dissolution *i.e.* by reducing the crystallinity of drug substances through formation of solid dispersions³.

However, there are practical limitations to these techniques. Although particle size reduction is commonly used to increase the dissolution rate, there is a practical limit to the size reduction that can be achieved by such commonly used methods as controlled crystallization and grinding. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wet ability^{4, 5}. Salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs which are weakly acidic or weakly basic may often not be practical.

Solid dispersions have been widely used to enhance the solubility, dissolution rate, and bioavailability of poorly soluble drugs. There are different types solid dispersion systems categorized according to the physical states of the drug and the carrier in the systems. It may be a molecular solid solution, a dispersion of amorphous or crystalline drug particles in an amorphous carrier matrix, or a combination of a solution and dispersion of solids. Spray drying is one of the techniques of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size. The large surface area of the resulting particle should result in an enhanced solubility and dissolution rate, consequently, improved bioavailability⁶.

Cyclodextrins are cyclic oligosaccharides, containing six, seven or eight glucopyranose units (α , β or γ respectively) obtained by the enzymatic degradation of starch. These are torus shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. Cyclodextrins are able to form complexes with poorly water-soluble drugs⁷⁻⁹. Thus they can enhance the solubility and bioavailability of such compounds. The aim of the present study was to improve the solubility and

dissolution rate of Ezetimibe by spray drying technique using different ratio of HP β -cyclodextrin.

MATERIALS AND METHODS:

Materials: Ezetimibe was a gift sample from Apollo Life Sciences Pvt. LTD, Mumbai India. HP- β -cyclodextrin was purchased from Roquette India Pvt. LTD, Mumbai. All other reagent and chemicals were analytical grade.

Method:

Physical Mixture: Sample for ratio optimization were prepared by mixing the drug and polymer in different ratio such as 1:1 to 1:4 w/w in the mortar for 5 min and then sieving¹⁰.

Preparation of Spray Dried Microsphere:

Ezetimibe microspheres were prepared by spray drying technique. Propanol was used as a solvent to prepare different drug/polymer ratio (1:1 to 1:4) microspheres. Feed solution was prepared by dissolving the drug and polymer in the solvent by using magnetic stirrer. Drug loaded microspheres were obtained by spraying the feed solution with a spray dryer (Lu, 222, Advanced, Lab ultima, Mumbai) using a standard 0.7mm nozzle. The solution was fed to the nozzle with a peristaltic pump, atomized by the force of compressed air and blown together with heated air to the chamber where the solvent in the droplets were evaporated. The dried microspheres were harvested from the apparatus collector and kept under vacuum for 48 hours^{11, 12}. The spray drying parameters are described in **Table 2**.

TABLE 1: FORMULATION COMPOSITION OF MICROSPHERES

Formulation code	Ratio (Drug – polymer)
F1	1:1
F2	1:2
F3	1:3
F4	1:4

TABLE 2: SPRAY-DRYING PARAMETERS

Inlet Temperature (°C)	Outlet temperature (°C)	Aspirator speed	Feed pump speed
100 – 120 °C	80 – 90 °C	40 - 50%	9-10 ml/min

Evaluation of Microspheres:

Determination of Percentage Yield and Drug Content: The percentage yield of each formulation

was determined according to the total recoverable final weight of microspheres and the total original weight of ezetimibe and HP- β - cyclodextrin. Microspheres (10mg) were triturated with 10ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml. After suitable dilution, Samples were measured at 231nm. Drug content was determined from standard plot^{13, 14}.

FTIR Spectroscopy: The interaction between the drug and polymers was determined by using the FTIR (8400 - Shimadzu, Japan) spectroscopy wherein infrared spectra of pure drug, physical mixture and pure drug loaded microspheres were carried out using the KBr disk method (2mg sample in 200mg KBr)¹⁵. The scanning range was 450 to 4000 cm^{-1} and the resolution was 1cm^{-1} .

Differential Scanning Calorimetry (DSC): A DSC study was carried out to detect possible polymorphic transition during the crystallization process. The thermal behavior of plain drug, drug loaded microspheres and blank microspheres were determined using differential scanning calorimeter (Mettler, Toledo) at heating rate of 10 $^{\circ}\text{C}/\text{min}$. The measurements were performed at a heating range of 50 – 250 $^{\circ}\text{C}$ under nitrogen atmospheres^{15, 16}.

X-ray Diffraction Study: X-ray diffractogram of the plain drug, blank microsphere and drug loaded microsphere were recorded by diffractogram using Philips X' Pert MPD diffractometer with Cu-K α line as a source of radiation which was operated at the voltage 35 kV and the current 25 mA. All samples were measured in the 2 θ angle range between 5 $^{\circ}\text{C}$ and 100 $^{\circ}\text{C}$ ^{15, 16}.

Particle Size Analysis: The microspheres were evaluated for the particle size. An optical microscope (Motic, B1, Series, Systemic Microscope) was used for this purpose. The microscope was equipped with the software, image manager through a camera. Analysis was carried out on the spray-dried microspheres dispersed in immersion oil. This slide was observed under the microscope. An image was clicked and used for the particle size analysis. The average particle size of the microspheres was expressed as the volume surface diameter (μm) and standard deviation (σ) was calculated for each batch of microspheres¹⁷.

Scanning Electron Microscopy (SEM): Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm spherical nature and surface topography of the crystals¹⁷.

Solubility Studies: Drug solubility was determined by adding excess amounts of pure Ezetimibe, their physical mixture and microspheres in distilled water and phosphate buffers 6.8 at 37 ± 0.5 $^{\circ}\text{C}$ respectively at a rotation speed of 100 rpm. The solution formed were equilibrated under continuous agitation for 24 h and passed through Whatman filter paper (No. 41) to obtain a clear solution. The absorbance of the samples was measured using UV spectrophotometer (UV 1800, Shimadzu, Japan) method at 231 nm and the concentrations in $\mu\text{g}/\text{ml}$ were determined. Each sample was determined in triplicate¹⁷.

In vitro Dissolution Studies: The dissolution of pure Ezetimibe, their physical mixture and microspheres was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai), Shimadzu, Japan. Dissolution medium was 900ml of pH 6.8 phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometer (UV 1800 Shimadzu, Japan) at 231nm. Each sample was determined in triplicate^{16, 17}.

Determination of the Physical Stability: To determine the physical stability of optimized Microspheres, a stability study of prepared Microspheres was carried out at 25 $^{\circ}\text{C}$ and 60% relative humidity for 6 months according to the ICH guidelines. The microsphere were packed in high density polyethylene (HDPE) container and placed in stability chamber (CHM-10S Remi, India). The samples were withdrawn at the interval of 0, 1, 3 and 6 months and evaluated for appearance, characterization by FT-IR and dissolution release and compared with initial results¹⁵.

Statistical Analysis: All analyses of data were performed with a statistical software package (SPSS 13, USA). The results are expressed as means and standard deviations. Comparative statistical studies on the inclusion complex and dissolution rate were performed by ANOVA.

RESULT AND DISCUSSION: Cyclodextrins (CDs) are cyclic oligosaccharides consisting of (α -1, 4)-linked α -D-glucopyranose units that contain a lipophilic internal cavity and a hydrophilic outer surface. The hydroxyl functions of the glucose are orientated to the exterior, which gives it hydrophilic character. The inner cavity is lined by skeletal carbons and etheral oxygen's of the sugar residues, which gives it a lipophilic character. These characteristics favour cyclodextrins to form inclusion complexes with a variety of host-guest molecules of suitable polarity and size. This characteristic of cyclodextrin is used to improve the pharmaceutical properties of numerous drugs such as solubility, dissolution, bioavailability and stability¹⁵. The spray drying method described here appeared to be a suitable and simple technique to prepare HP- β -Cyclodextrin microspheres loaded with Ezetimibe. It is a one-step process, easy and rapid, as it combines drying of the feed and embedding of the drug into a one-step operation. The spray dried microspheres formulations were collected and found to be free-flowing and white in colour.

TABLE 3: PERCENTAGE YIELD AND DRUG CONTENT OF MICROSPHERES

Formulation code	Percentage yield (%)	Drug content (%)
F1	79.85	94.11 \pm 0.12
F2	65.64	95.27 \pm 0.23
F3	86.56	98.34 \pm 0.17
F4	79.13	96.34 \pm 0.09
PM1	-	88.27 \pm 0.32
PM2	-	91.42 \pm 0.12
PM3	-	92.12 \pm 0.06
PM4	-	94.22 \pm 0.18

Mean \pm SD, n = 3

Percentage Yield and Drug Content: The percentage yield of spray dried microspheres of different ratios of drug-polymer was found to be in the range of 79-84%. Drug content for the spray dried microspheres of different ratio of drug-polymer formulation was found to be in the range of 93-99 % \pm 0.013 (**Table 3**).

Fourier Transform Infra - Red Spectroscopy (FTIR): Fourier transform infrared spectroscopy has been used to assess the interaction between carrier and drug molecule. The FTIR spectrum of ezetimibe, HP- β -cyclodextrin and microsphere prepared by spray dried technique shown in (**Fig. 1, 2**). In IR spectra of ezetimibe the O-H stretching in alcohols occurs at 3239.72 cm^{-1} , the C-H stretching in alkanes at 2909.49 cm^{-1} , the C=O stretching in carboxylic acids occurs at 1714.12 cm^{-1} , the C-N stretching in amine occurs at 1217.03 and the C-F stretching in alkyl halides occurs at 1066.65 cm^{-1} , the C=C stretching in benzene ring occurs at 1508.93.

In IR spectra of HP- β -cyclodextrin the O-H stretching in free hydroxyl occurs at 3401.06 cm^{-1} , the C-H stretching in alkanes occurs at 2929.89 cm^{-1} , the C=O stretching in ethers occurs at 1653 cm^{-1} , the C-O stretching in ethers occurs at 1032.36 cm^{-1} . In IR spectra of microsphere the O-H stretching in alcohols occurs at 3287.40 cm^{-1} , the C=O stretching in carboxylic acids occurs at 1729.80 cm^{-1} , the C-C stretching in aromatics occurs at 1508.02 cm^{-1} , the C-H stretching in aromatic occurs at 1397.07 cm^{-1} , the C-F stretching in alkyl halides 1027.29 cm^{-1} .

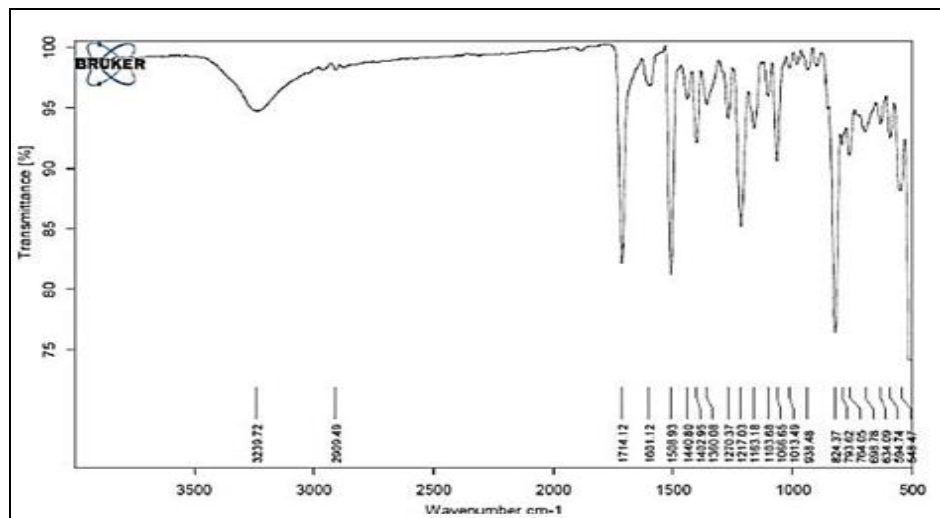


FIG. 1: FTIR SPECTRUM OF EZETIMIBE

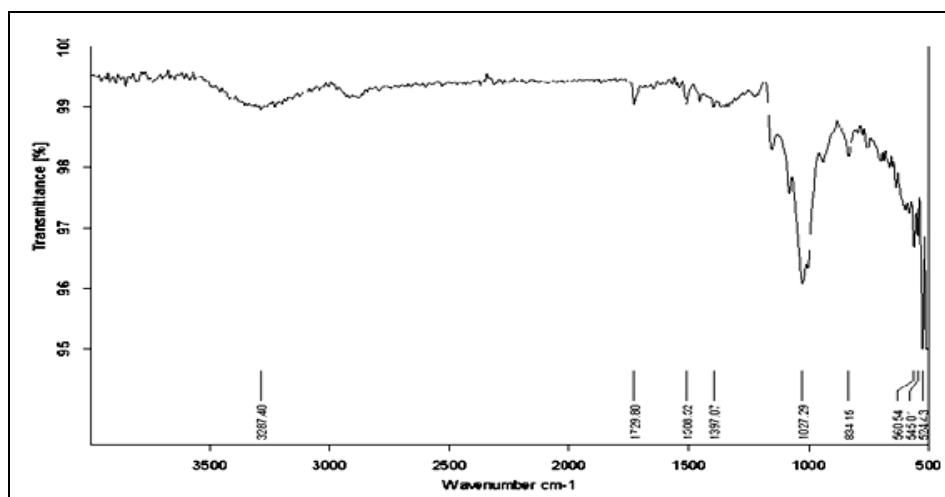


FIG. 2: FTIR SPECTRUM OF THE EZETIMIBE MICROSPHERE PREPARED WITH HP-β-CYCLODEXTRIN

Differential Scanning Calorimetry (DSC): The DSC thermogram of ezetimibe, HP-β-cyclodextrin and its microsphere prepared by spray dried method as shown in (Fig. 3, 4) respectively. The DSC curve of ezetimibe exhibited a sharp endothermic peak at 163.66 °C corresponding to its melting point. The DSC curve of HP-β-

cyclodextrin showed a broad endothermic peak at 120.35 °C. The heat content of Ezetimibe was found to be -178.32 mJ and for HP-β-cyclodextrin it was -748.21 mJ respectively. The melting point and heat content of microsphere of ezetimibe with HP-β-cyclodextrin in the ratio (1:3) was found to be 160.13 °C and -3.37 mJ.

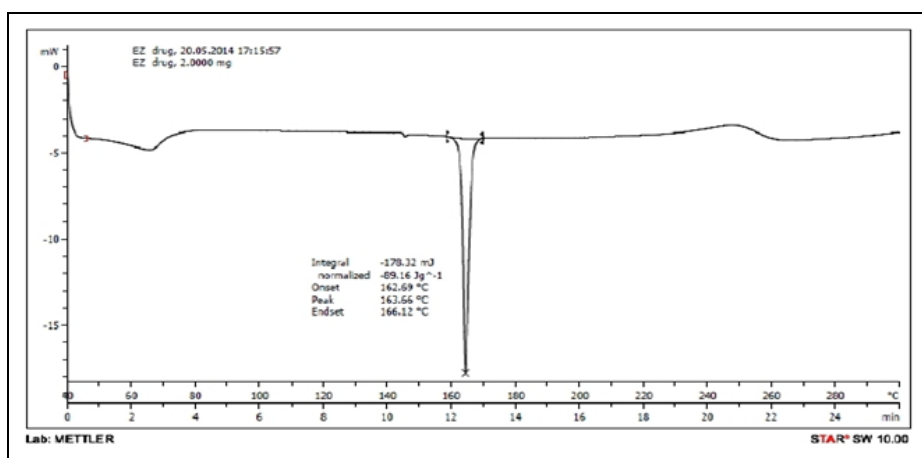


FIG. 3: DSC THERMOGRAM OF EZETIMIBE

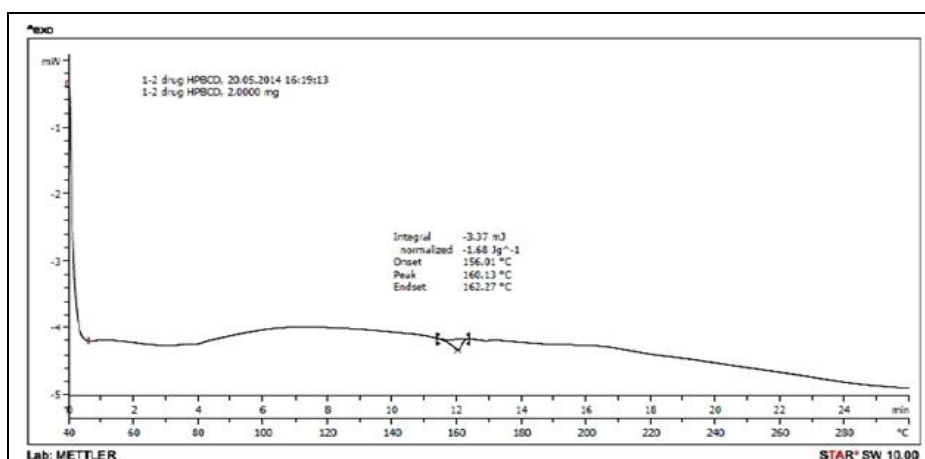


FIG. 4: DSC THERMOGRAM OF THE EZETIMIBE MICROSPHERE PREPARED BY SPRAY DRIED METHOD WITH HP-β-CYCLODEXTRIN

X-ray Diffraction (XRD): Powder X-ray diffraction spectroscopy has been used to assess the degree of crystallinity of the given sample. XRD patterns are shown in (Fig. 5, 6). The X-ray diffraction pattern of ezetimibe exhibited sharp, highly intense and less diffused peaks indicating

the crystalline nature of ezetimibe. HP- β -cyclodextrin showed diffused peaks because of its amorphous nature. The X-ray diffraction pattern of microsphere prepared by spray dried method of ezetimibe with HP- β -cyclodextrin showed less intense and highly diffused peaks.

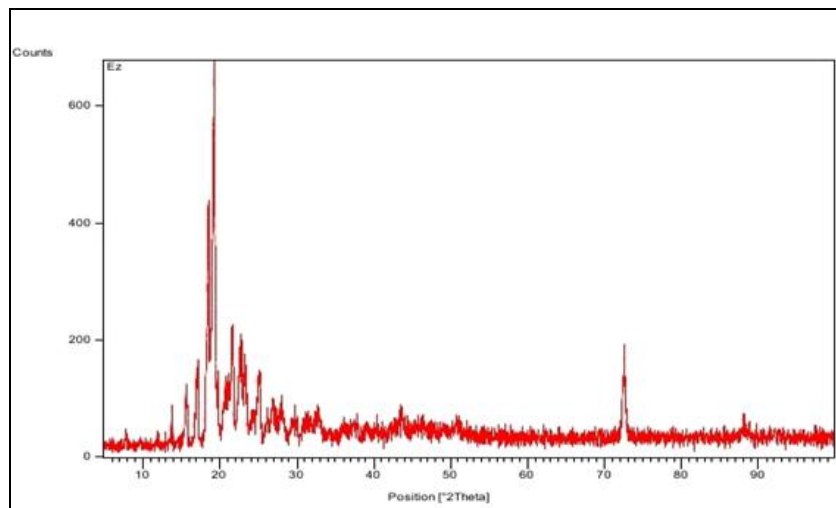


FIG. 5: XRD OF EZETIMIBE

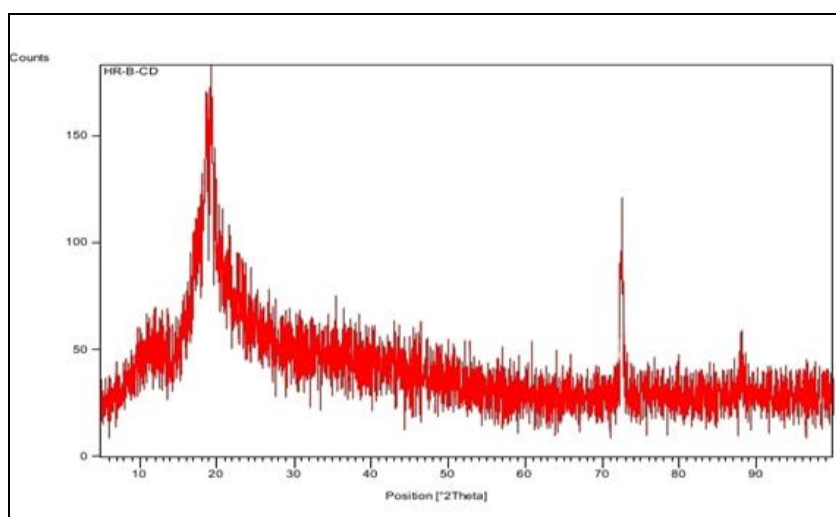
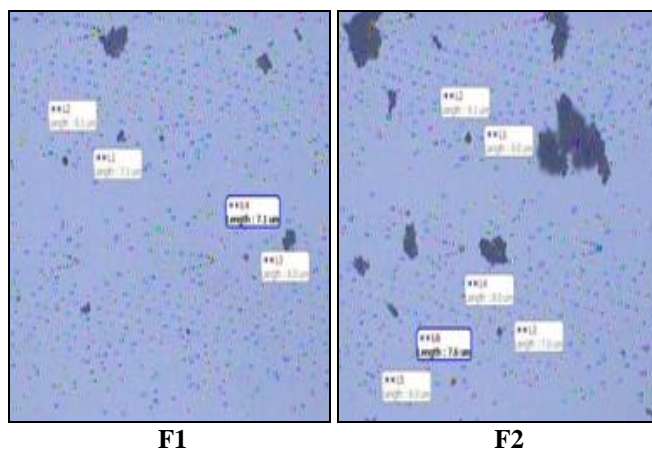


FIG. 6: XRD OF THE EZETIMIBE MICROSPHERE PREPARED BY SPRAY DRIED METHOD WITH HP-B-CYCLODEXTRIN

Particle Size Analysis: Average particle size of microspheres ranged from 1 to 100 μ m, such particles are considered to be suitable for oral administration (Fig. 7). It was also noted that increasing drug to polymer ratio, slightly increased the size of microspheres (Table 4).

TABLE 4: PARTICLE SIZE OF MICROSPHERE

Formulation Code	Average Particle size (μ m)
F1	7.1
F2	7.8
F3	8.0
F4	8.6



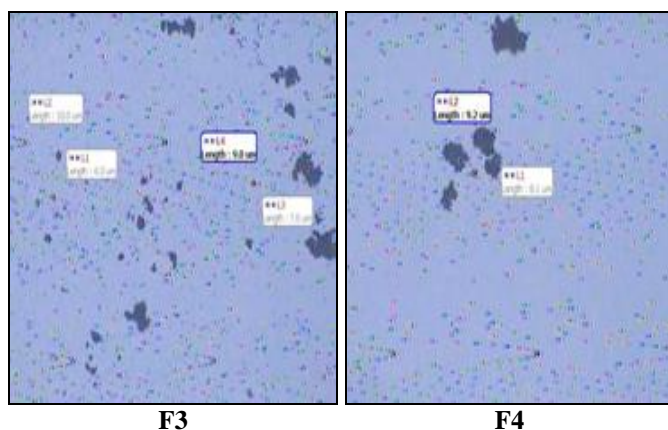


FIG. 7: OPTICAL MICROSCOPIC IMAGES OF FORMULATION

Scanning Electron Microscopy (SEM): The spray dried microspheres was analyzed by SEM for studying particle shape and surface structure (Fig. 8, 9). The shape of prepared microspheres are uniform and spherical in shape with small in size 7-9µm (Table 4). The spherical shape of microspheres does not lead to cake formation during storage because of less point of contact thereby increasing the stability of the microsphere formulation, which is an advantage over other shapes. This could be therefore, indicate that Ezetimibe particle size has been reduced, which also accelerates solubility and dissolution.

From the Fig. 9, it is concluded that Ezetimibe particles were needle, plate shaped with smooth surface, while in case of spray dried microspheres it was observed that they were of irregular shape and size. Fig. 10 clearly shows that crystal shape of Ezetimibe was completely changed in microspheres. SEM images show that the crystalline Ezetimibe is converted to its amorphous form which was confirmed by DSC and XRD study.

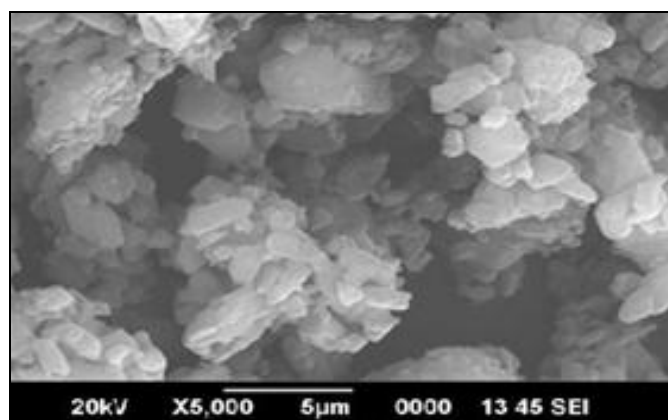


FIG. 8: SEM IMAGE OF EZETIMIBE

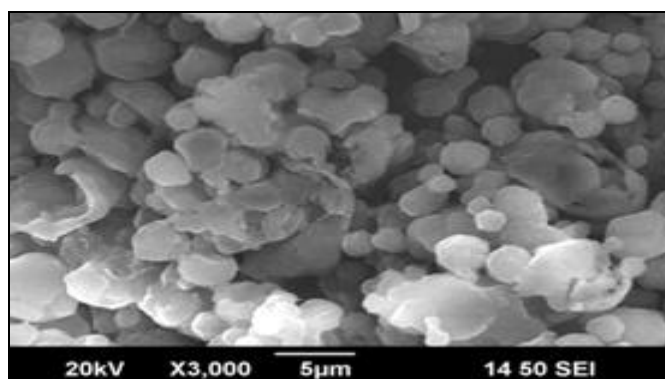


FIG. 9: SEM IMAGE OF MICROSPHERES SOLUBILITY STUDIES

Increase in the solubility of Ezetimibe from microspheres (0.94g/mL) was found to be nearly three times higher than the solubility of the pure drug (0.31mg/mL) in Phosphate buffer 6.8, suggesting the presence of a high amount of an amorphous form of Ezetimibe in the microspheres, indicating super-saturation. Increase in the solubility of Ezetimibe from the physical mixture (PM) was nearly two times higher than pure drug. This could be due to the solubilising effect of highly water-soluble HP-β-cyclodextrin used in the formulation. The solubility results for the different formulations are shown in Table 5. The higher solubility of Ezetimibe from Microspheres may be due to wetting, increase in surface area and solubilizing effect HP-β-cyclodextrin which could reduce the interfacial tension between ezetimibe and dissolution medium.

TABLE 5: SOLUBILITY OF EZETIMIBE AND DIFFERENT FORMULATION IN DISTILLED WATER AND pH 6.8

Different formulation	Solubility in distilled water (mg/ml)	Solubility in phosphate buffer pH 6.8 (mg/ml)
Pure drug	0.27± 0.021	0.31± 0.015
F1	0.52± 0.017	0.58± 0.046
F2	0.70± 0.031	0.75±0.025
F3	0.78±0.042	0.82±0.035
F4	0.87± 0.013	0.94±0.024
PM1	0.30±0.027	0.36±0.014
PM2	0.36±0.047	0.44±0.019
PM3	0.54±0.034	0.57±0.024
PM4	0.61±0.028	0.64±0.025

Mean ± SD, n = 3

Dissolution Study: The dissolution profile of pure Ezetimibe, physical mixture and prepared microspheres in pH 6.8 phosphate buffer shown in Fig. 10. The dissolution profiles were plotted as the % release from the different microspheres versus

time in minute. It was observed that the release rate from pure Ezetimibe and physical mixture was very slow and incomplete compared with spray dried microspheres. The % release from ratio of (1:3 w/w) drug and polymer showed more release compared to other ratios. In case of microspheres containing (1:3 w/w) showed 99% release in 90 min and at the same ratio of physical mixture showed 68% release in 90 min.

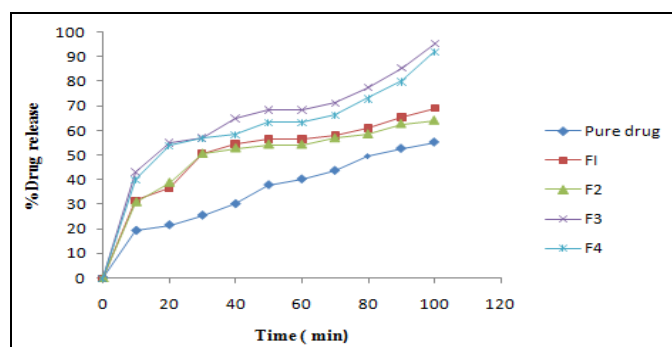


FIG. 10: *IN VITRO* RELEASE OF EZETIMIBE FROM MICROSPHERES BY SPRAY DRYING

TABLE 6: STABILITY DATA OF SPRAY DRIED MICROSPHERES

Testing interval	Description of Drug	FT-IR Study	XRD Study	% Drug Loading	<i>In vitro</i> drug release
Initial	White to off white	As Standard	As standard	70.36±0.012	99.23±0.023
1 month	Complies	Complies	Complies	69.28 ± 0.02	98.39±0.034
3 month	Complies	Complies	Complies	69.02 ±0.045	98.12 ±0.013
6 month	Complies	Complies	Complies	68.89±0.056	98.09±0.019

Mean ± SD, n = 3

CONCLUSION: In this present investigation revealed that Ezetimibe can form spray dried microsphere with HP-β-cyclodextrin. From these result, it can be assumed that the formation of the spray dried microsphere with HP-β-cyclodextrin can increase the aqueous solubility of Ezetimibe. The improved dissolution rate may be due to increase in solubility, brought about by wetting and solubilizing effect of the HP-β-cyclodextrin, which could reduce the interfacial tension between the Ezetimibe and the dissolution medium and amorphizing power of HP-β-cyclodextrin.

The solubility and dissolution of the spray dried microspheres was improved significantly compared with its physical mixture and pure sample of Ezetimibe. The Ezetimibe microspheres containing 1:3 w/w (ezetimibe: HP-β-cyclodextrin) showed highest % of drug release and solubility compare to other ratio, physical mixture and pure sample of Ezetimibe. Stability results data showed that

The increase in dissolution from the microspheres and physical mixtures was probably due to the wetting, solubilizing effect and amorphizing power of HP-β-cyclodextrin, which could reduce the interfacial tension between the Ezetimibe and the dissolution medium, thus leading to a higher dissolution rate than pure Ezetimibe. The large surface area of the resulting microspheres should result in an enhanced dissolution rate and thereby improve the bioavailability.

Determination of the Physical Stability: The best way to guarantee stability is by maintaining their physical state and molecular structure. The results of the stability study of prepared microspheres (1:3 w/w) of Ezetimibe Stored at 25 °C and 60% relative humidity for 6 month is presented in **Table 6**. Prepared microspheres of Ezetimibe were stable and within acceptable limit with all the properties when compared to initial results of prepared microspheres of Ezetimibe.

prepared microspheres stable for 6 month as per ICH guidelines and no significant change compared to initial result. Hence, from the above result it can be concluded that spray dried microspheres of ezetimibe is a useful technique to improve the solubility and dissolution of poorly water soluble drug like Ezetimibe.

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CONFLICTS OF INTEREST: Nil

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