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FORMULATION AND EVALUATION OF HYDROTROPIC SOLID DISPERSION OF ELUXADOLINE

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Keywords:

Hydrotropic solid dispersion, Eluxadoline, Sodium caprylate, *In-vitro* drug release

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ABSTRACT: In the present research, newly developed hydrotropic solid dispersion technique utilizing the use of aqueous solvent was developed, to avoid the utilization of organic solvent and all together declining their toxicity. This technology was employ intended for preparing the dispersion of Eluxadoline by using new hydrotropic agent sodium caprylate with using different ratio. Prepared formulations were evaluated by Solubility study, Fourier transforms infrared spectroscopy, X-Ray Diffractometry, Drug content analysis, and *in-vitro* drug release study. Based on the evaluation of hydrotropic solid dispersion concluded that the concept or technology of hydrotropic solid dispersion method is a novel, nontoxic and as well cost-effective technique for the rationale of enhancing the aqueous solubility of substance and bioavailability of poorly water-soluble drugs. The improvement within solubility and dissolution of Eluxadoline is a clear sign. It can be able to use in the future for more poorly water-soluble drugs to enhance solubility and also which having low bioavailability is a major problem.

INTRODUCTION: Product development scientists frequently meet significant difficulties in solving the problem of poor water solubility of drug applicant in the growth of pharmaceutical dosage form. A few decades ago, 40% new drug failures in development had been recognized poor biopharmaceutical properties, as well as water insolubility. A solid dispersion of one or more active pharmaceutical ingredients in an inert and nontoxic carrier matrix at solid state by using solvent evaporation method, melting-solvent method, fusion method [1, 2]. In 1961, Obi and Sekiguchi developed a useful system whereby numerous of the limits by the bioavailability improvement of low water-soluble drugs can be overcome.

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Drugs with having low aqueous solubility will mostly show less dissolution rate, as well as incomplete absorption and drugs with having poor membrane permeability, will exhibit penetration rate-limited absorption.

There are strategies of pharmaceutical study that focuses on improving oral bioavailability of drug are:

- Enhancing the aqueous solubility and percent drug release of low water-soluble drugs.
- Enhancing the permeability of low permeable drugs [3].

Hydrotropic Solid Dispersion: Hydrotropic solid dispersion methods prohibit the make use of organic solvent for the formulation of solid dispersion [4]. Hydrotropic agents are water-soluble, while the drug is poorly water-soluble. Though, in the occurrence of a huge amount of hydrotropic agents in the water, the drugs get solubilized. After that, water is evaporated by a suitable evaporation method to get a solid mass that is solid dispersion.

Then, prepared solid dispersions can be denoted as HSDs [5]. Sodium caprylate act as a hydrotropic agent and use for enhancing the solubility of low aqueous soluble drug [6].

Eluxadoline drug used in the cure of irritable bowel syndrome [7, 8] and recently approved by USFDA in 2015 [9]. It is practically insoluble in water (0.00268 mg/mL) and having low oral bioavailability (1.02%) [10].

MATERIALS AND METHODS:

Materials: Eluxadoline was provided by Torrent Pharmaceuticals Limited, Ahmadabad. Sodium caprylate was purchased from S.K. Traders' M. P. and further reagents and chemicals used during formulation were analytical grade.

Methods:

Physical Identification and Melting Point: Physical identification of drug was visually recognized, and the melting point of Eluxadoline was determined by using the capillary method and compared with reference data that is shown in **Table 1** [11].

Determination of Solubility of Eluxadoline: Solubility study of Eluxadoline was carried in demineralized water, methanol, and water: acetonitrile (50:50). Drug added in the excess amount and slowly to 5 ml of each solvent. Then, solutions shaken on the mechanical shaker on room temperature for 12 h. Solutions were allowed for 24 h for obtained equilibrate. Then, the solutions were transferred into the centrifuge tubes and centrifuged on about 1000 rpm for 5 min and filtered by using filter paper and obtained filtrates were correctly diluted. The prepared diluted solutions analyzed at 243 nm by using a suitable blank solution.

Selection of Ratio of Drug and Carrier in Hydrotropic Solid Dispersion: There was a significant improvement in the solubility of drug-using a sodium caprylate in the ratio of 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6. So that optimized formulation based on solubility. Finally, ratios of the drug: carrier (1:4) used for solid dispersions.

Preparation of Solid Dispersions: For the formulation of solid dispersion, accurately weighed the quantity of the drug was dissolved into the hydrotropic solution and then, stirred on the magnetic stirrer at room temperature for 4 to 6 h. After evaporating of the solvent obtained solid mass was transferred to glass plate. Then, dried in an oven at a temperature of 50 °C for 24 h. After drying, solid mass was crushed and then, triturated using a pestle mortar and then, passed through sieve no # 80 and store in a closed container [12, 13, 14].

FT-IR Study of Pure Drug, Physical Mixture, and Solid Dispersion Preparations: For all the prepared formulations and Eluxadoline, the pellets have been prepared using potassium bromide (KBr) for FT-IR study. The samples were analyzed in 'Agilent FTIR spectrometer. IR spectra analyzed which are illustrated in **Fig. 4** and **5** [15].

X-Ray Diffraction Studies: The powder X-ray diffraction spectra of Eluxadoline, prepared solid dispersion and the physical mixtures were done using Bruker D8 Advance X-ray diffractometer. The x-rays of wavelength 0.154 nm were used. (Analysis was done from UGC DAVV Consortium, Indore).

Drug Content Analysis: Accurately weighed solid dispersion equivalent to 50 mg of Eluxadoline transferred to 100 ml volumetric flask and dissolved into 6.8 phosphate buffer and made volume with the same solution up to the mark. After suitable dilution, the absorbance of the above sample was measured at 243 nm using 6.8 phosphate buffer as a blank solution and then, by using calibration curve drug content of Eluxadoline was calculated [16, 17].

***In-vitro* Release Studies:** Accurately weighed 50 mg of sample was used for the dissolution study. The sample has been withdrawn by predetermined time intervals and analyzed intended for *in-vitro* drug release by measuring the absorbance at 243 nm using phosphate buffer pH 6.8 as a medium. The volume was withdrawn at each one-time intervals and replaced by using the same amount of fresh medium.

RESULTS AND DISCUSSION:

Physical Identification and Melting Point: Physical Identification of a drug was visually identified, and the melting point of Eluxadoline was determined by the capillary method.

TABLE 1: PHYSICAL APPEARANCE AND MELTING POINT OF ELUXADOLINE

S. no.	Properties	Standard	Drug
1	Color	White Amorphous powder	White Amorphous powder
2	Odor	Odorless	Odorless
3	Melting point	187-189 ºC	188-189 ºC

The results of solubility studies of Eluxadoline are summarized in **Table 2**.

TABLE 2: SOLUBILITY OF ELUXADOLINE

Solvent	Solubility (mg/ml)	Description
Water	0.00230	Practically insoluble
Methanol	0.00866	Practically insoluble
Acetonitrile : water (50:50)	1.47	Slightly soluble

The solubility of solid dispersion in difference ratio was obtained in various solvents using UV spectrophotometer and optimized formulation based on solubility. The solubility of 1:4 (Eluxadoline: sodium caprylate) have the highest solubility when compare with different ratio of solid dispersion and shown in **Table 3**.

TABLE 3: SOLUBILITY OF SOLID DISPERSION

S. no.	Solid dispersion (Eluxadoline : Hydrotropic agent)	Solubility (mg/ml)
1	1:0	0.00230
2	1.1	1.44
3	1:2	1.64
4	1:3	2.6
5	**1:4**	**2.8**
6	1:5	1.5
7	1:6	1.017

IR Spectrum of Eluxadoline, sodium caprylate, physical mixture, and solid dispersion shown in **Fig. 1, 2, 3, 4,** and there was no important change in the peak value with sodium caprylate in case of solid dispersion when compare with the physical mixture. Thus, it can be concluded that the sodium caprylate interferes in IR is compactable with Eluxadoline.

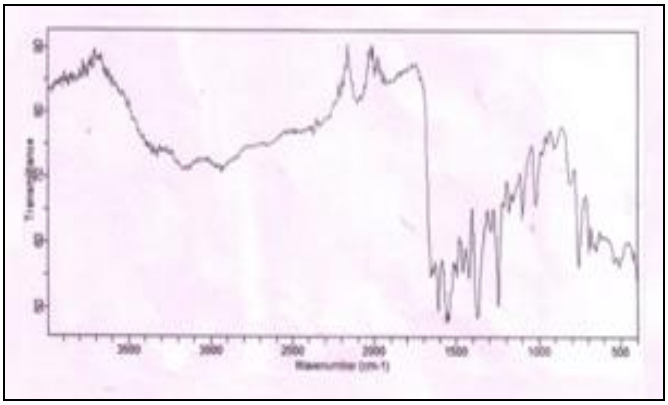

FIG. 1: IR SPECTRUM OF ELUXADOLINE

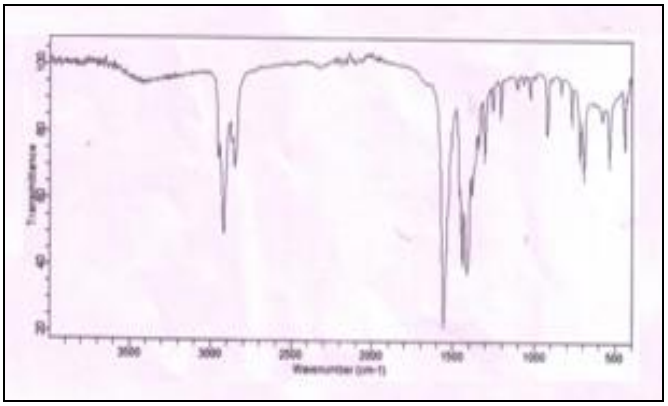

FIG. 2: IR SPECTRUM OF SODIUM CAPRYLATE

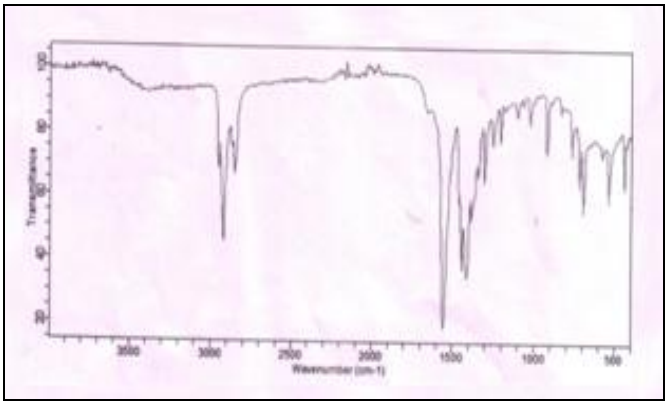

FIG. 3: IR SPECTRUM OF PHYSICAL MIXTURE

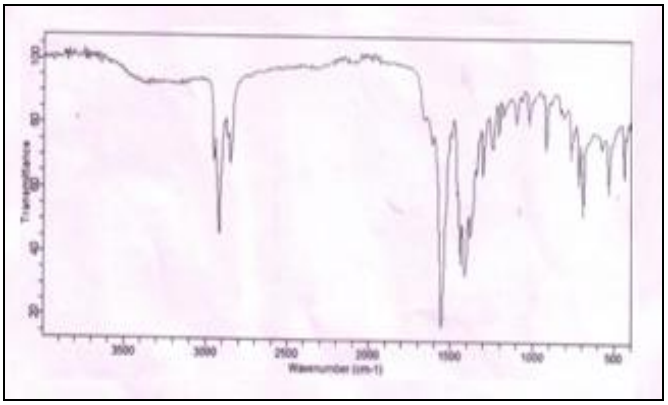

FIG. 4: IR SPECTRUM OF SOLID DISPERSION

The amorphous nature of Eluxadoline was verified by the feature XRD pattern **Fig. 5** with peak and also the XRD patterns of solid dispersion, and the physical mixture gave sharp and strong peaks shown in **Fig. 7, 8**. It was observed that the total number of peaks in solid dispersion was less than

in PM mixture. Also here was a decrease in the intensities of the characteristic peaks in solid dispersion. This recommended that the degree of amorphousness in case of solid dispersion is more.

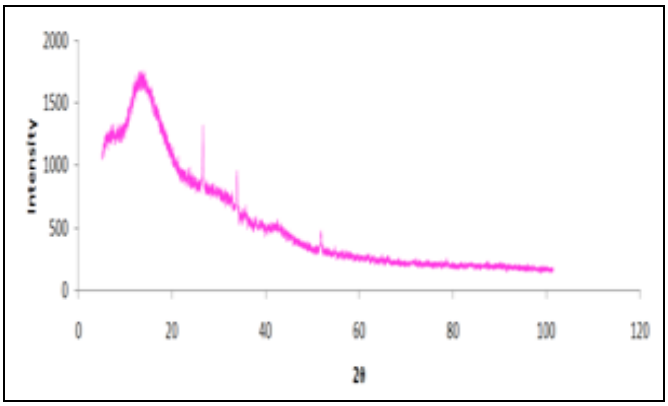

FIG. 5: XRD OF ELUXADOLINE

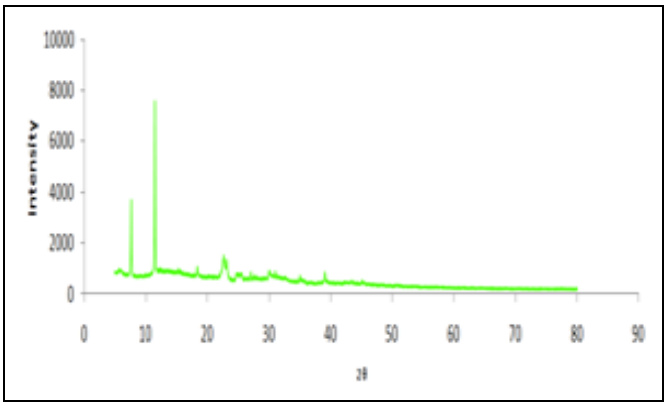

FIG. 6: XRD OF SODIUM CAPRYLATE

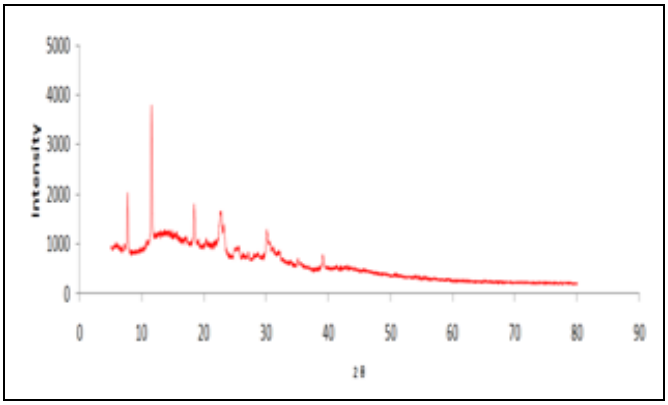

FIG. 7: XRD OF PHYSICAL MIXTURE

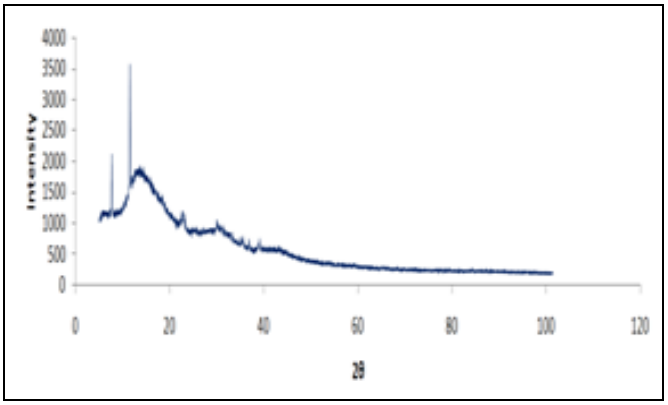

FIG. 8: XRD OF SOLID DISPERSION

TABLE 4: DRUG CONTENT OF SOLID DISPERSIONS

S. no.	Composition	Drug content (%)
1	Eluxadoline : Sodium Caprylate (1:1)	88.00 ± 0.26
2	Eluxadoline : Sodium Caprylate (1:2)	93.0 ± 0.10
3	Eluxadoline : Sodium Caprylate (1:3)	95.89 ± 0.77
4	Eluxadoline : Sodium Caprylate (1:4)	97.30 ± 0.32
5	Eluxadoline : Sodium Caprylate (1:5)	93.70 ± 0.15
6	Eluxadoline : Sodium Caprylate (1:6)	89.74 ± 0.45

Drug content of solid dispersion was as shown in **Table 4,** and it indicated that the drug is uniformly dispersed in the powder formulation. Therefore, the solvent evaporation method suitable for the formulation of solid dispersion.

The formulation of hydrotropic solid dispersion of Eluxadoline with different ratio sodium caprylate screened for the selection of suitable ratios. Above all the formulations, the ratio of Eluxadoline: Sodium caprylate (1:4) showed maximum dissolution rate within three minute and data shown in **Table 5**.

TABLE 5: *IN-VITRO* DRUG RELEASE

S. no.	Batch	Time in minutes							
		1	2	3	4	5	10	20	30
1	F1	62.76 ± 0.50	64.16 ± 0.54	65.53 ± 0.36	65.07 ± 0.58	65.53 ± 0.97	69.6 ± 0.25	65.53 ± 0.30	65.5 ± 0.30
2	F2	67.38 ± 0.33	68.76 ± 0.70	70.61 ± 0.62	71.07 ± 0.59	70.15 ± 0.58	70.61 ± 0.53	71.07 ± 0.53	71.07 ± 0.98
3	F3	76.14 ± 0.12	77.07 ± 0.95	78.46 ± 0.29	79.38 ± 0.27	78.92 ± 0.53	79.38 ± 0.33	79.84 ± 0.51	79.38 ± 0.25
4	F4	86.3 ± 0.50	90.46 ± 0.16	99.69 ± 0.45	99.23 ± 0.43	98.76 ± 0.51	99.69 ± 0.44	99.23 ± 0.37	98.76 ± 0.13
5	F5	80.7 ± 0.51	81.23 ± 0.57	82.61 ± 0.52	83.53 ± 0.52	84 ± 0.51	83.53 ± 0.30	84 ± 0.43	84 ± 0.085
6	F6	76.61 ± 0.41	77.53 ± 0.45	78.46 ± 0.55	79.38 ± 0.94	79.84 ± 0.16	79.38 ± 0.47	79.84 ± 0.54	79.38 ± 0.52

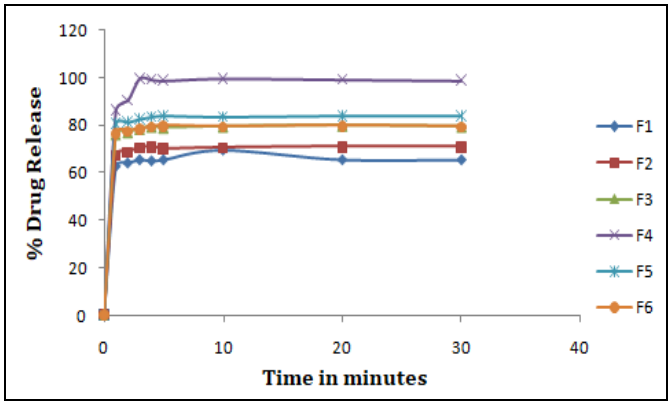

FIG. 9: *IN-VITRO* DRUG RELEASE

CONCLUSION: Solid dispersion of Eluxadoline was developed with the idea of hydrotropic solid dispersion technique. Solid dispersion of eluxadoline containing sodium caprylate as a hydrotropic solid dispersion shows the fast release of drug as compare to the pure drug, the quick onset of action which improved absorption of Eluxadoline after oral administration of the drug.

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CONFLICTS OF INTEREST: Declaration confirming the absence of any conflict of interest. We authors, the undersigned research article entitled "Formulation and evaluation of hydrotropic solid dispersion of eluxadoline" submitting the article. We confirm that we do not have any conflict of interest in connection to the proposed research project.

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