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ORIGINAL RESEARCH ARTICLE

Formulation and Evaluation of Spherical Crystal of Etoricoxib

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ABSTRACT

The purpose of this study was to prepare spherical crystal of poorly water soluble drug of Etoricoxib and to know the effect of different polymers on the solubility and dissolution rate of Etoricoxib by using acetone, water, and chloroform as bridging liquid. The Quassi emulsion solvent diffusion technique was mainly used for the method of agglomeration. The polymers like ethyl cellulose, polyvinyl pyrrolidone (PVP K30) were used in spherical agglomeration process. The pure drug and its agglomerates are characterized by Fourier Transform infra red spectroscopy (FTIR).The FTIR studies indicated that there is no chemical changes in the agglomerates of Etoricoxib.The spherical agglomerates with different polymers exhibited increasing in the saturation solubility and dissolution rate. The spherical agglomerates have lower micromeric properties as compared to pure drug. The spherical agglomerates exhibited excellent dissolution rate (82.58 % in 75 minutes) as compared to Etoricoxib. The agglomerates also exhibited higher micrometric properties which indicate good compressibility and packability characteristics.

Key words: Etoricxib, Agglomerates, dissolution, Ethyl cellulose, polyvinyl pyrrolidone, micrometric properties, FTIR

INTRODUCTION

Combinatorial chemistry is the modern technique which is used to screening of new drugs. Many of the drugs evolving from this technique are categorized under Biopharmaceutics classification system (class 2) drugs [3]. These drugs are poorly water soluble and easily absorbed through gastrointestinal membrane. Therefore for improvement of bioavailability for oral administration is to enhance the dissolution rate. So for this a special technique is used for improvement of oral bioavailability is spherical crystallization.[4] This technique was first proposed by Kawashima, Y., et al. Spherical crystallization was defined "it as an agglomeration process that transforms crystals directly into compact spherical forms during the crystallization. It also enables co-precipitation of drug and encapsulating polymer in the form of spherical particle [7]. Theresultant crystals can be designated as spherical agglomerates. Spherical crystallization is aneffective alternative to improve dissolution rate of drugs [6, 7] this can be achieved by various methods such as spherical agglomeration, quasi-emulsion solvent diffusion, and neutralization method[8]Agglomerates exhibit improved secondary characteristics, like flowability and compressibility, so that direct tabletting or coating is possible without further processing (mixing, agglomerates, sieving, etc). Etoricxib (Fig 1) is a nonsteroidal anti-inflammatory drug (NSAID) is having the highest COX 2 selectivity which is used in the treatment of osteoarthiritis and rheumatoid arthritis, acute gouty arthritis, dysmenorrheal, acute dental surgery, pain and similar condition without affecting platelate function or damaging gastric mucosa [9]. The major drawback of etoricoxib isdry mouth aphthous ulcers, taste disturbances and paresthesis. Etoricoxib shows low aqueous solubility hence to improvement of aqueous solubility is a valuable goal to improve therapeutic efficacy [10] Apart from the particle size enlargement, this technique has also been applied for various purposes such as taste masking and particle size enlargement [7-10].The main purpose

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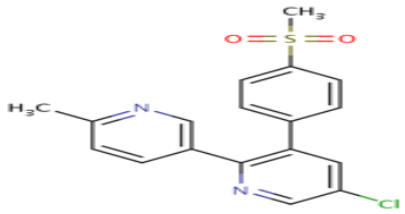
of this work was to improve the solubility, dissolution rate, micrometric properties of Etoricoxib by Quassi emulsion diffusion technique

Fig 1- Structure of Etoricoxib



MATERIALS AND METHODS

Etoricoxib was a free sample of Cadila Health Care Limited, Ahmadabad, Gujarat, India polyvinylpyrrolidone (PVP K 30), ethyl cellulose, chloroform, acetone, hydrochloric acid obtained as CDH, New Delhi. All other chemicals are analytical grade.

Preparation of calibration curve of Etoricoxib:

Standard stock solution:

The standard stock solution was prepared by dissolving 10 mg of drug in 5ml of methanol to get a concentration of 1000mcg/ lt. It was appropriated diluted with methanol to get a concentration of 100mcg /lt and was kept as stock solution.

Determination of λ_{max}:

The standard solution of etoricoxib was scanned in UV spectrophotometer (ELICO SL 159)to obtain the maximum Wavelength absorption against blank between wavelength of 200-400 nm. The standard solution was scanned for absorbance maxima against blank. The maximum absorbance was found to be 234 nm.

Preparation of calibration curve:

The stock solution of etoricoxib was accordingly diluted to obtain concentration range of 0-10 µg/ml. The absorbance was observed against methanol as blank and the calibration curve was plotted between concentration (x axis) and absorbance (y axis)

Preparation of spherically agglomerated solid dispersion of Etoricxib:

All spherical agglomerates were obtained by the quasi emulsion solvent diffusion method. Spherical agglomerates were prepared with and without stabilizers by spherical crystallization technique. The stabilizer composition was given in Table 1 Etoricoxib (1gm) was dissolved in good solvent acetone. The bridging liquid chloroform was added to it. The resulting solution was then poured drop wise in to the poor solvent distilled water)containing different stabilizers like PVP, EC with a stirring rate of 1000 rpmusing propeller type agitator (Remi Motors Ltd., Mumbai, India) at room temperature. Afteragitating the system for 0.5 h, the prepared agglomerates were collected by filtration through filter paper the spherical crystals were washed with distilled water and driedin a desiccator at room temperature.

Table 1- composition of spherically agglomerates of Etoricoxib

Ingredients	F1	F2	F3
Etoricoxib(gm)	1	1	1
Acetone(ml)	5	5	5
Ethyl cellulose	-	0.75	-
polyvinylpyrrolidone	-	-	0.75
Chloroform	1	1	1
Distilled water	75	75	75

Fourier Transform Infrared studies:

The Fourier Transform infrared (FTIR) spectra of powder and the agglomerates were recorded on an FTIR spectrophotometer (IR AFFINITY 1, SHIMADZU)

Evaluation of Spherical Agglomerates:

Morphology / Description:

The prepared crystals from the formulations (F1, F2, and F3) were taken in three different previously cleaned glass slides and distributed uniformly as a thin layer on the slides. Then the slides were shown under the microscope and were represented in the (Figure No.3, 4, and 5)

Micrometric properties:

The particle size distribution was studied by the sieve analysis method [12].The shape of the crystals was observed under an optical microscope. The loose bulk density (LBD) and tapped bulk density test apparatus. Carr's index and Hauser's ratio were calculated using LBD and TBD values [13].The angle of repose was accessed by foxed funnel method and the saturation solubility study was carried out by UV spectrophotometric method by using 0.45µm membrane filter and the amount of drug dissolved is analyzed.

Drug content:

50 mg of Etoricoxib crystal was dissolved in 10 ml methanol in a volumetric flask. To it HCl buffer was added to make desired volume. By Shaking and well mixing the solution was filtered through a filter paper. From the filtrate 1 ml was taken and made up to 10 ml with the same buffer. The solution was than analyzed under UV spectrophotometer at λ max 234 nm.

***In vitro* dissolution studies:**

The *in vitro* dissolution studies were carried out using 8 stations USP 2 dissolution

Testing apparatus (Lab India).The dissolution medium used was 900 ml of 0.1N HCl. The dissolution medium was kept at in a thermostatically controlled water bath at 37±0.5 0C. The agglomerates and pure drug containing10 mg of Etoricoxib were weighed and introduced into the dissolution medium. The medium was stirred at 75 rpm using paddle. At predetermined time intervals 5 mL of samples were withdrawn and analyzed spectrophotometrically. At each time of withdrawal 5 mL of fresh corresponding medium was replaced into the dissolution bowl. The cumulative amount of drug release was calculated and plotted against time.

RESULTS AND DICUSSIONS

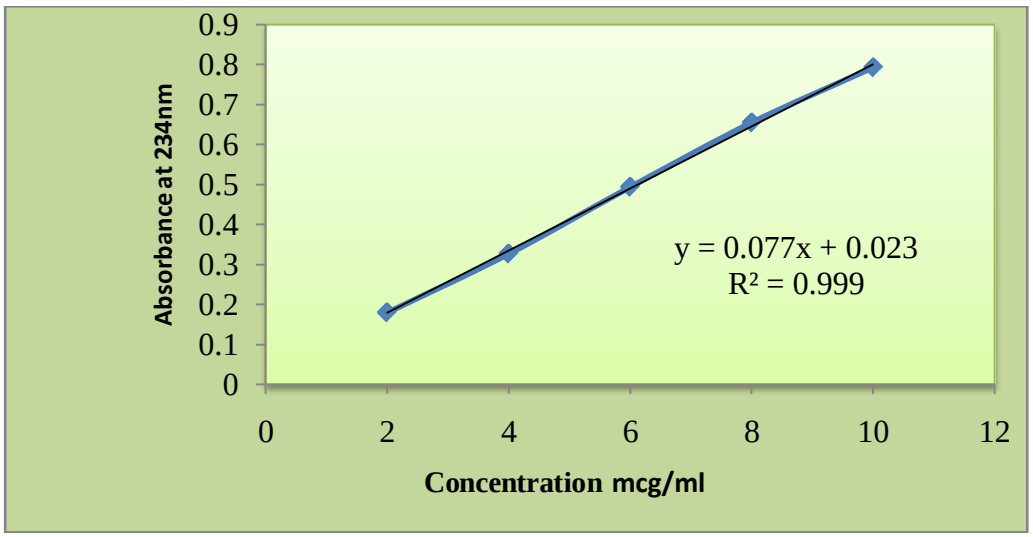
Calibration curve:

The absorbance for the different concentration (0-10 µg/ml) was recorded at 234nm and the regression equation of the calibration curve was found to be y=0.077x+0.023 the calibration curve was shown in (**Fig.2**) and represented in (**Table 2**)

Table. 2- Absorbance value for the calibration curve of Etoricoxib

Conc. of drug(µg/ml)	Absorbance at 234 nm
0	0
2	0.180
4	0.321
6	0.494
8	0.655
10	0.793

Fig.2-Calibration curve of Etoricoxib



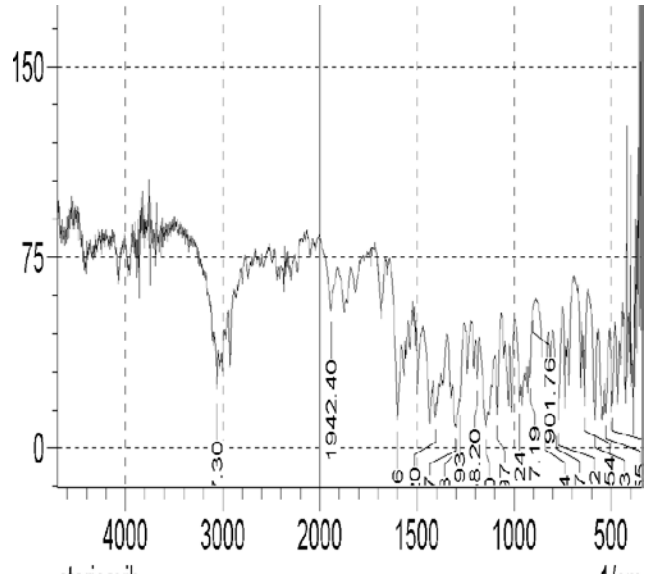
Quasi Emulsion Solvent Diffusion Method:

Spherical agglomerates of Etoricoxib were prepared by quasi emulsion solvent diffusion method (QESD) using solvent system. It involves solvent system and a bridging liquid. The selection of these solvent depends on the solubility of drug in individual solvent. Accordingly acetone water were selected as a good solvent, chloroform is selected as bridging liquid etoricoxib is highly soluble in acetone, but poorly soluble in water. Hence, this solvent system was used in the present study. In QESD method, when good solvent solution of drug plus bridging liquid were poured in the solvent(containing different stabilizers) under agitation, quasi emulsion droplets of bridging liquid and good solvent were produced. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplets induces the crystallization of the drug within the droplet due to the decrease in solubility of the drug in the droplet containing the poor solvent. The bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by coalescence of these dispersed crystals. In the present study effect of different stabilizers on solubility and dissolution rate of spherical agglomerates of Etoricoxib were studied.

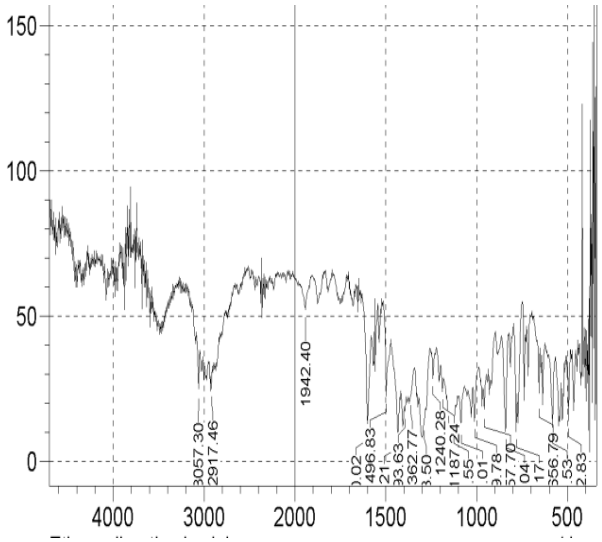
FTIR studies:

The possible interaction between drug and different stabilizers used was studied in Fourier Transform Infrared Spectroscopy the FTIR spectrum of etoricoxib and different stabilizers and the spherical agglomerates of etoricoxib were are shown in (**Fig 3**). The FT-IR spectra of spherical crystal formulation did not show the presence of any additional peaks for new functional groups. The major peaks of the drugs

remained unchanged in the mixture. These results suggest absence of any chemical interaction between the drug (ETR) and the polymers used in spherical crystal formulation. Hence, the drug was found to be compatible with all the excipients used in the formulations.



a)



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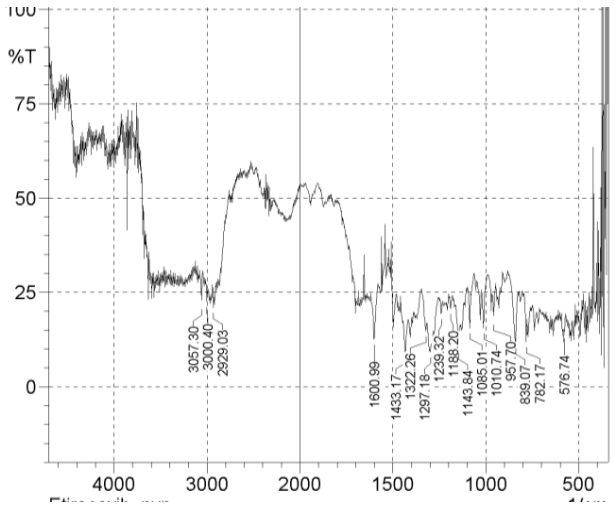

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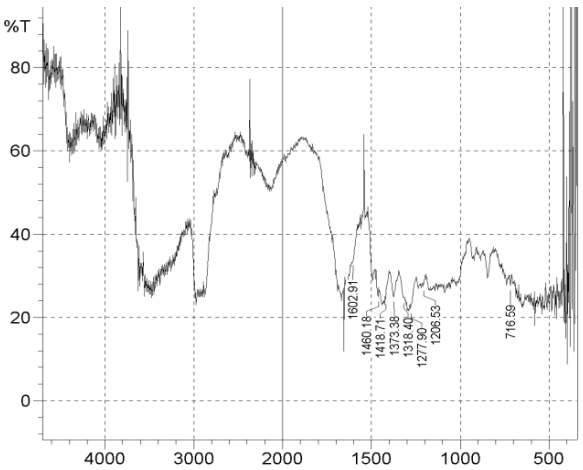

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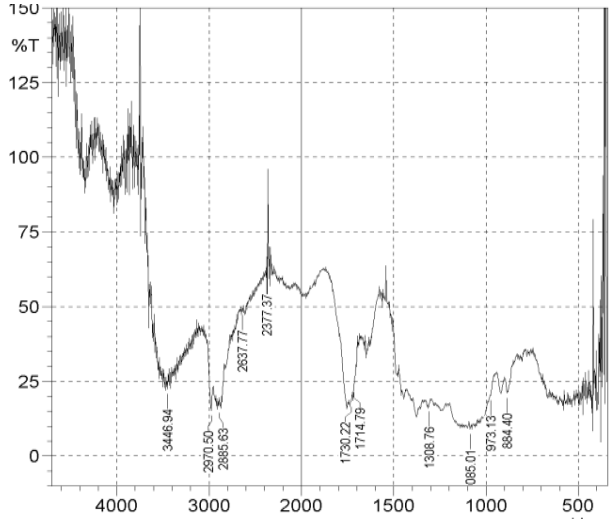

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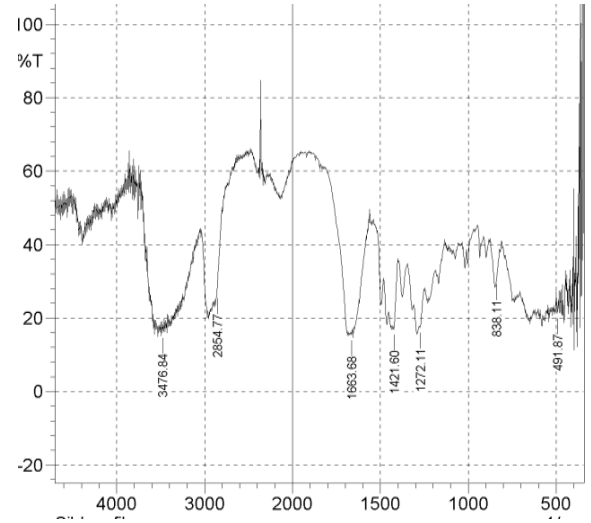


f)

Fig 3 – FTIR Spectra of a) Etoricoxib b) Etoricoxib + Ethyl cellulose(F2) c)Etoricoxib + polyvinyl pyrrolidone(F3) d) polyvinyl pyrrolidone + Ethyl cellulose e)Ethyl cellulose f) polyvinyl pyrrolidone.

Morphology /Description

The different formulation (F1, F2, and F3) were morphologically described means of color, shape and odour which represented in (**Table 3**) indicates the pure drug was amorphous/ floppy while the formulations were irregular, partial and spherical.

Table 3-Morphology of spherical agglomerates of Etoricoxib

Morphology	F1	F2	F3
Color	Pale yellow	Pale yellow	Pale yellow
shape	Irregular/ spherical	Spherical lumps	spherical

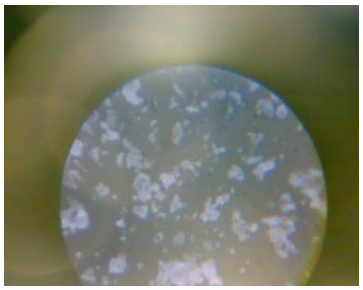


Fig 4: Formulation 1

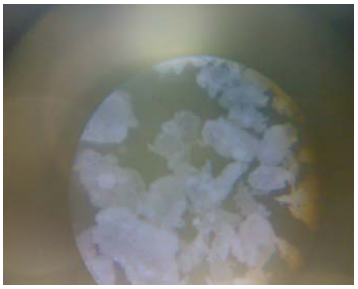


Fig 5: Formulation 2

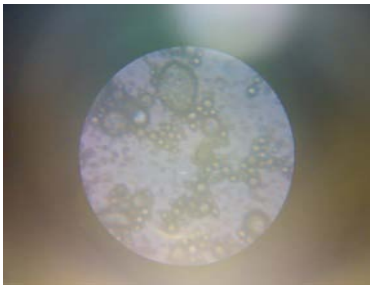


Fig 6: Formulation 3

Micromeritic properties

The results of Carr's index, Hausner's ratio, angle of repose are presented in (**Table 4**). These parameters were used to assess the packability, flow and compressibility properties of the agglomerates. The Carr's index, Hausner's ratio, Angle of repose value values for pure drug of Etoricoxib was 29.93%, gmL^{-1}, 24.62%, gmL^{-1}, 35.87° respectively, indicating poor flow and packability properties. On the other hand, all prepared spherical agglomerates exhibited higher Carr's index, Hausner's ratio and Angle of repose as compared to pure drug. It also has good compressibility which indicates good packability. The prepared agglomerates exhibit low cars index, Hausner's ratio and angle of repose as compared to pure drug. The saturation solubility studies indicate that the pure drug having the least solubility while as the formulations have the higher solubility.

Table 4-Micromeritic, solubility data for spherical agglomerates

samples	Cars index (%)	Hausners ratio (%)	Angle of repose (°)	Solubility in water(μgmL^{-1})
Etoricoxib	29.93	24.62	35.87	0.19
F-1	18.64	5.91	22.61	1.89
F-2	22.78	9.35	33.36	2.4
F-3	15.62	1.07	21.39	3.12

Drug content

Drug content and percentage yield was carried out to know the any drug lose during formulation the results were represented in (**Table 5**). Yield for the formulations were within the range of 68.41-87.93% and drug content was 75.98-87.28%

Table 5-Drug Content and Percentage yield

Formulations	% yield	Drug Content
F1	79.36	83.52
F2	68.41	75.98
F3	87.93	87.28

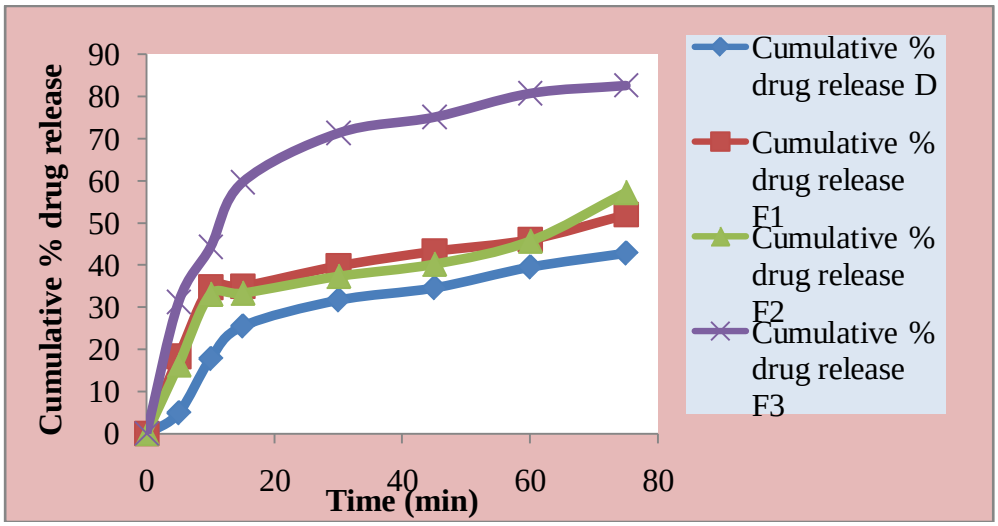
In Vitro dissolution studies

The results of in vitro dissolution studies are shown in (**Fig 6& Table 6**).Pure Etoricoxib exhibited least dissolution pattern compared to formulations at five minutes only 4.87 % of drug goes into solution while at 75 minutes it was 42.78 %. The formulation F3 shows highest dissolution of 31.16 % in five minutes and 82.58 % in 75 minutes. So among all these polymers PVP K 30 shows better effect on dissolution rate and solubility compared to other formulations. The drug release sequences are F3>F1>F2>Pure drug. This indicates the improved solubility and dissolution rate of Etoricoxib Formulations.

Table 6 – cumulative % drug release different formulations

Time(min)	Cumulative % drug release			
	Pure Drug	F1	F2	F3
0	0	0	0	0
5	4.87	18.31	16.29	31.16
10	17.74	34.77	33.06	44.23
15	25.46	34.99	33.32	59.61
30	31.65	39.83	37.32	71.29
45	34.56	43.31	40.2	75.07
60	39.48	46.09	45.67	80.71
75	42.78	51.98	57.21	82.58

Fig 6-Dissolution profile of pure drug and its agglomerates in 0.1N HCl



CONCLUSION

The present research shows that the spherical agglomerates of Etoricoxib was prepared by using different polymers like Ethyl Cellulose and PVP K 30 shows an excellent improvement in solubility and dissolution rate also to improving micromeritic properties. This technique may be applicable for producing oral solid dosage form of Etoricoxib with improving dissolution rate, bioavailability and physiochemical properties.

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