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Research Article

EFFECT OF PROCESS PARAMETERS ON THE PHYSIOMECHANICAL PROPERTICS OF ACECLOFENAC LOADED MICROPARTICLES

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ABSTRACT

Extended-release aceclofenac micro particles were prepared liquid system by emulsion solvent evaporation method, in which the Aerosil was employed as an inert dispersing carrier to improve the dissolution rate of aceclofenac, and Eudragit RSPO as a retarding agent to control the release rate. In order to avoid local gastrointestinal irritation, one of the major side effects of non steroidal anti-inflammatory drug after oral ingestion. The process of preparation involved the use of acetone as good solvent, dichloromethane as a bridging liquid, water as poor solvent Aerosil as anti adhesion agent, and sodium deodecyl sulfate to aid in the dispersion of the drug and excipients into the poor solvent and assessment of viscosity of oil phase .The resultant micro particles were evaluated for the recovery, bulk density, average particle size, drug loading, and incorporation efficiency. And the factors affecting the formation of micro particles and the drug release rate were investigated. It was observed by a scanning electron microscope (SEM) that the micro particles were finely spherical and uniform, and no entire aceclofenac crystals were observed visually. The results of X-ray diffraction indicated that aceclofenac in micro particles was disordered; suggesting that aceclofenac was highly dispersed in microparticles.The drug loading of micro particles was enhanced with increasing the ratio of drug to excipients, and the incorporation efficiency was always >79%.The dissolution profile could be modulated with adjusting the amount of retarding agent and dispersing carrier has an important role in the formulation.

Keywords: Emulsion solvent evaporation method, Aceclofenac (Ac), Eudragit RSPO (Eu RSPO), Aerosil, Sodium deodecyl sulfate (SDS).

INTRODUCTION

Aceclofenac is a potent non steroidal anti-inflammatory drug (NSAID) used for its analgesic, anti inflammatory properties in humans. Irritation of the gastro intestinal tract (GIT) with most NSAIDs is one of the major side effects reported after oral administration of aceclofenac. since its gastro intestinal intolerance is not only related to the inhibition of the prostaglandin synthesis, but also to acute local contact of the drug with the gastric mucosa, the development of an enteric multi particulate drug delivery system might reduce or even avoid the mucosal irritation[1]. The objective could be achieved by formulating aceclofenac – loaded micro particles, which after several additional advantages including Good reproducibility of transport through the GIT and minimization of local damage to the GIT mucosal membrane because of the wide distribution over a large area with large monolithic dosage forms [2,3,4].

Several process parameters involved in the emulsion-solvent evaporation method, like nature and amount of dispersing agents, aqueous and organic phase volumes, stirring rate of emulsion system, affect the final micro particle properties [5, 6, 7]. Dispersing carrier has an important role in the production of micro particles. They decrease the interfacial tension between the lipophilic and hydrophilic phase of the emulsion[8]. During the solvent evaporation process, the gradual removal of the solvent from the polymer droplets is an accompanied by a corresponding decrease of the volume and the increase of the viscosity of the individual droplets[9]. Highly viscous droplets particularly coalesce must faster than they can divide. Droplet coalescence and particle coagulation can usually be overcome the use of a small amount of a suitable dispersing agent [10, 11]. It provides a thin protective layer around the droplets and hence reduces the extent of their collision and coalescence.

In the general micro encapsulation technique using on o/w emulsion system (e.g. Solvent evaporation method)[12, 13]. The drug is dissolved, dispersed or emulsified in an organic polymer solution, which is then emulsified in an external aqueous or oil phase. As the organic solvent is removed by evaporation, the drug and polymer are precipitated in the droplets thus forming the micro particles [14]. In the phase separation method, the polymer is precipitated around a dispersed drug phase through the addition of a non solvent an incompatible polymer, or a temperature change [15]. This method results in the formation of micro particles (core shell structure) versus micro spheres (matrix structure) formed by the solvent evaporation method. Several micro encapsulation of the methods are available too the preparation of the drug delivery system [16]. Which depend primarily on the drug solubility in the polymeric materials. They are essentially based on solvent evaporation methods and phase separation.

The method presented here leads to micro particles composed of a bio compatible inert oily core containing aceclofenac, a non steroidal anti-inflammatory drug (NSAID), and a bio compatible polymer such as Eu RSPO [17]. The applicability of the emulsion solvent evaporation process depends on the successful entrapment of the active agent with in the micro particles [18]. The presence of an inert organic oil dissolving Aceclofenac during the process enables the formation of core-shell systems. Further more, it could prevent the drug from crystallizing at the micro capsule surface [19], implying a better efficiency of the drug delivery system.

In this present study, the principles of above two methods were combined to design the Extended-release micro particles having solid dispersion structure for poor water-soluble drug. In this manufacturing process, the preparation of the micro particles and the solvent evaporation system were combined into one step. Aerosil, as an inert solid dispersing carrier, was introduced in this formulation to improve the dissolution rate of poorly water-soluble drug and the controlled-release polymer Eu RSPO was employed to bind the inert solid dispersing carrier into micro particle and control the drug-release rate. And it was indicated that the present method could also be used to improve the micromeritics properties of solvent evaporation system with simple preparation process. The influence of the nature of the low boiling good solvent of the polymer, the high boiling poor solvent (inert oil), the surfactant concentration, the stirring rate, the dispersed phase viscosity and volume of continuous phase on the diameter and size distribution of micro particles was studied.

MATERIAL AND METHOD

Aceclofenac was purchased from sigma chemical co., Mumbai, India. Eudragit RSPO (Mn=33800g/mol batch no.-5673), Aerosil 200 (colloidal Silicon dioxiale), cobot sanmer Ltd.All other chemicals, such as sodium dedecyl sulfate (SDS), dichloromethane, acetone, etc.were of analytical grade.

Preparation of Aceclofenac – loaded micro particles by emulsion-solvent evaporation method

Aceclofenac (0.1 g) was dissolved with Eudragit RSPO (0.3g) in a mixed solution of acetone (good solvent 8 ml), and dichloromethane (bridging liquid 12 ml). Then Aerosil (0.3g) was suspended uniformly in the drug-polymer solution under vigorous agitation. The resultant drug-polymer-Aerosil suspension was poured into 150ml distilled water containing 0.02-0.15% of SDS (poor solvent) under agitation (400-700rpm) and thermally controlled at 8-38^{0}c. After agitation the system for 20 min, another 150ml of poor solvent was added slowly and agitation was continued for another 40 min till the translucent emulsion droplets turned into opaque micro particles. The solidified micro particles were recovered by filtration and washed with water. The resultant products were dried in an oven at 50^{0}C for 6hrs [20].

To investigate the factors affecting recovery, micro particles properties and drug release behaviors of micro particles more easily, the general preparation condition of micro particles was employed as follows except mentioned especially. The amount of drug, Eu RSPO, and Aerosil in formulation was 0.1, 0.3, and 0.5 g. The volume of acetone and CH_2Cl_2 was 8 ml and 12ml, respectively, and the concentration of SDS in distilled water was 0.08%. The agitation speed and temperature was 700 rpm and 8-30^{0}C.

The recovery of the micro particles was determined from the ratio of the amount of 196-520µm micro particles to that of loaded powders. The X-ray diffractometer (D/max-r A type, Rigau, Japan) was employed to investigate the dispersion state of Aceclofenac in the micro particles produced at different ratios of the drug to excipients.

Evaluation of Aceclofenac Micro Particles

Assessment of viscosity of oil phase

The viscosities of oil phase were evaluated using an Ostwald viscometer at room temperature (30 ± 2ºC. The absolute viscosities of that solution were expressed in mPa.s.

Entrapment efficiency

Aceclofenac was extracted from micro particles after dissolving the polymer of micro particle using acetonitrile and sonicated for 2hours.filtered the resultant solution through what man Filter No 41. Absorbance of the resultant solution was recorded by UV-VIS spectrophotometer (Lambda 25, Perkin Elmer, and Germany) at 275nm.

Microencapsulation efficiency was determined using the following relation:

Microencapsulation efficiency = Estimated practical percentage drug content ×100 / Theoretical percentage drug content

Particle size analysis and surface morphology of micro particles

Surface morphology of Aceclofenac ethyl cellulose was studied using a scanning electron microscope (ISM 5610 LV SEM, JEOL, Datam Ltd, Tokyo, Japan). Samples were prepared on a 10 × 10 mm brass stub and coated with gold using a sputter coater (Joel auto fine coater, Japan) at accelerating voltage of 20kv at the high vacuum mode. Particle size analysis of the micro particles was carried out using a Malvern particle size analyzer (Malvern instruments, Mastersizer 2000, U.K.). Approximately 10mg of micro particles was suspended in 5ml of MilliQ water and analyzed with an obscuration index of ~5 % (measure of amount of light lost due to induction of sample against light path).

Drug release study

In vitro release study of Aceclofenac micro particles was carried out in 900ml of phosphate buffer (pH 7.2) maintained at 37±0.5ºC, with stirring speed 100rpm, using auto sampling US dissolution apparatus type 1(rotating basket) [DS8000 Disso Sr.No:0826533 Lab India]. Micro particles, equivalent to 50 mg of Aceclofenac were used for the study. 10 ml samples were withdrawn at pre-determined time intervals, filtered through a 0.45µm membrane filter, diluted suitably and analyzed using a UV spectrophotometer at 275nm.

RESULTS AND DISCUSSION

Preparation process of the Aceclofenac micro particles with Eu RSPO and Aerosil

When the drug-polymer-Aerosil suspension was poured into poor solvent with stirring the finely dispersed gel-like emulsion droplets were formed immediately. Due to the good affinity of the polymer to the organic solvent, good solvent (acetone) and bridging liquid (dichloromethane) in the droplets could not be diffused into poor solvent at once. Because good solvent, which is discretionarily miscible with poor solvent, was diffused out from the emulsion droplets under the agitation, drug and polymer in the droplets were supersaturated, precipitated, and deposited on the aerosil gradually. Consequently, the droplets were consolidated into micro particles by the linkage action of bridging liquid. The diffusion of good solvent into poor solvent to achieve diphase equilibrium between the droplets and poor solvent. After the process for 20min, 150ml of poor solvent was added into the system to promote the diffusion speed of good solvent and part of bridging liquid. Further solidification of the droplets led to production of the micro particles. The solidified micro particles was filtrated, washed and dried to eliminate the residual organic solvent. The formation of the micro particles could be described in the following process: the formation of emulsion droplets, the diffusion of the organic solvent and the solidification of the droplets. The scheme of the preparation process was illustrated in Fig 1.

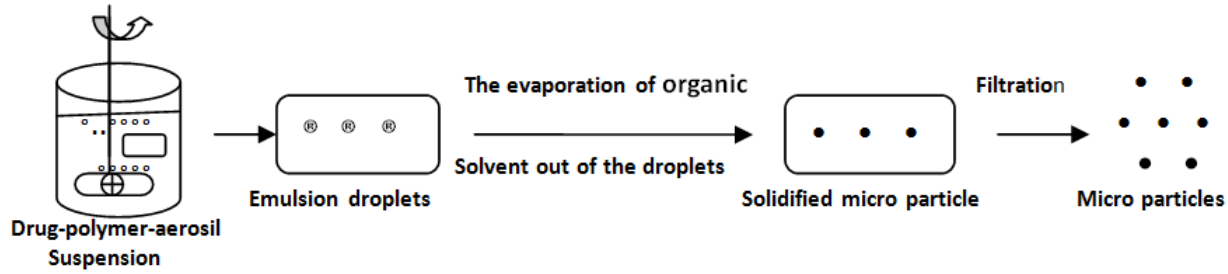


Fig. 1: It shows Scheme of the preparation process and mechanism

The preparation process of the present micro particles was almost similar with that of drug-Eudragit micro particles [21] except that Aerosil was introduced in this micro particles formulation as an inert solid dispersing carrier to improve the dissolution rate of aceclofenac. Due to its large surface area, high porosity, and unique adsorption properities, Aerosil has been successfully used as dispersing agents to increase the dissolution rate of sparingly soluble drug [22]. At the same time, Aerosil was an effective anti adhesion agent, and it could accelerate the solidification of droplets and be packed in the higher recovery of micro particles could be obtained comparing with other conventional method of micro particles.

In this formulation, Eu RSPO was used as a bond and retarding agent in order to bind the aerosil into micro particles and control the release rate. In the previous research [21] for the preparation of

microparicles with Eu RSPO using quasi-emulsion solvent diffusion method, a large ratio of drug to Eu RSPO and also a large amount of organic solvent had to be used, since the polymer was easy to be precipitated as a fibrous aggregate or adhere to the equipment because of its high viscosity. In this study, however, this problem could be avoided effectively due to the good anti adhesion property of Aerosil. And it was found that the micro particles having a good spherical shape were easy to form under strong agitation, though the plasticizer was not added in this formulation. It was indicated that Eudragit RSPO was one of the suitable polymer for the preparation of micro particle using this method due to its good plastic deformation property.

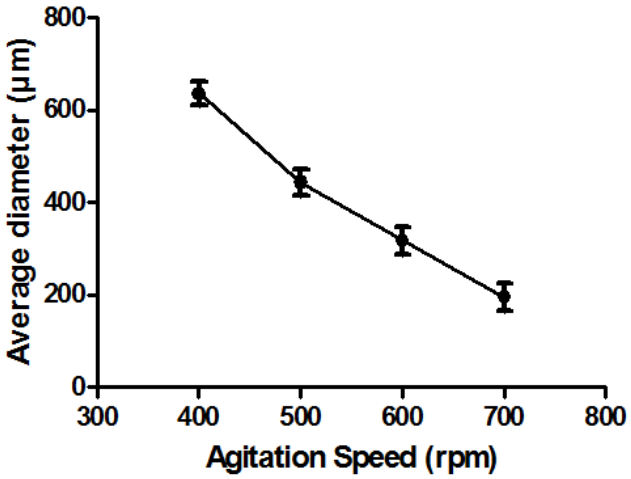


Fig 2. It shows the relationship of the average diameter of micro particles and the

Agitation speed at 35˚C temperature of the system

The size of the micro particle was mainly controlled by the agitation speed under a certain temperature.Practically; the agitation speed greatly affected the size of the emulsion droplets in the initial stage, which determined the diameter of the resultant micro particles. The diameter of the emulsion droplet was determined by the balance between the interfacial tension of the emulsion droplets and the shearing force applied to the droplets under agitation. It was illustrated that the higher speed of the agitator formed the smaller droplets because of the increase in shearing force applied as shown in Fig 2.

The surface morphology and internal structure of the micro particles were investigated using a SEM. As seen in Fig 3, the micro particles were invariably spherical and exhibited porous surface with a large number of interstices, while no entire aceclofenac crystals were observed visually. The Aerosil particles and amorphous like polymer were proper mix uniformly in dense texture, and macro-pores and voids were observed in the internal matrix. It was assumed that the co precipitation of drug and polymers occurred on the surface of the emulsion droplets and then the film like a shell was formed on the outer surface of droplets. The cavity and micro particles due to the further diffusion of the organic solvents out of the droplets.

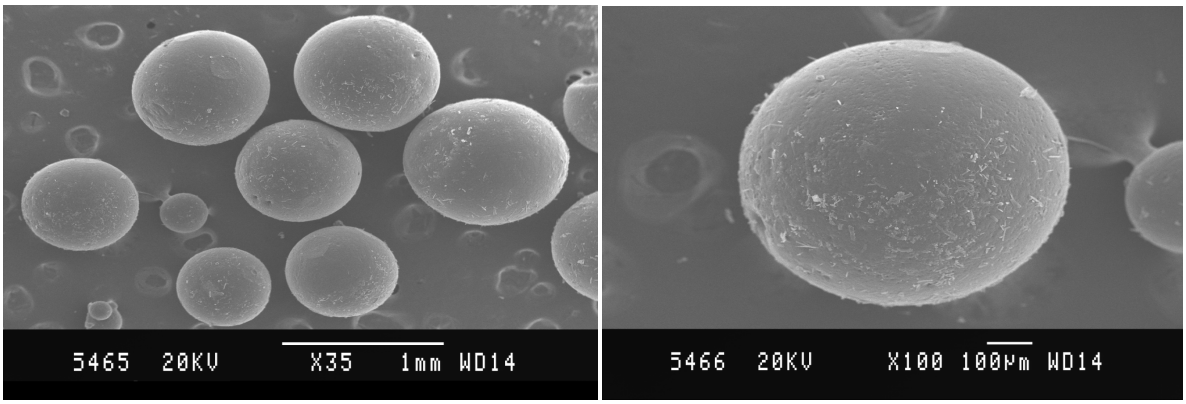


Fig. 3: It Shows Scanning electron microphotographs of micro particles

Effect of the amount of dichloromethane, acetone, and sodium dedecyl sulfate (SDS) on micro particles properties

The influence of the amount of CH_2CL_2, acetone and the concentration of SDS in distilled water on recovery, micromeritics properties of micro particles was show in Table 1.

To investigate the effect of bridging liquid on the micro particles properties, the amount of acetone, and the concentration of SDS in distilled water was fixed at 5ml and 0.08%, respectively. And the amount of dichloromethane was varied between 0 and 12ml for the preparation of the micro particles. As can be seen in Table 1,without dichloromethane was added, no micro particles was obtained after the drug-polymer-Aerosil suspension was poured into poor solvent ,because acetone was diffused into poor solvent so rapidly that no emulsion droplet could be formed. When the amount of dichloromethane was increased to 12ml, the finely dispersed spherical emulsion droplets could be seen in poor solvent under the agitation.

However, the emulsion droplets were adhered together and were turned into some big lumps immediately when the stirring was discontinued. Consequently, no micro particles could be recovered. It was believed to be due to the leaving superfluous CH_2Cl_2 in the droplets were not solidified completely. Though a part of dichloromethane could be diffused into poor solvent, most of it's remained in the droplets due to its limited solubility in poor solvent. The recovery of micro particles was >75%.These suggested that the initial stage of preparation but also the solidification of drug and polymer in droplets.

Table 1: It shows the effect of the volume of CH_2Cl_2, Acetone, and viscosity of the dispersed phase and the concentration of SDS in continuous phase on micro particle properties

Volume of Dispersed Phase DCM/AC	Viscosity of Dispersed phase	SDS %w/w	% yield	D_{50} (µm)
0:8	0.5047	0.08	-	-
11.:9	0.3563	0.08	71.9±0.01	245.35
13:7	0.3458	0.08	73.1±0.02	319.27
18:5	0.1398	0.08	-	-
12:8	0.3426	0.08	76.8±0.01	265.32
12:6	0.3744	0.08	70.4±0.04	339.16
12:7	0.3683	0.08	73.6±0.04	328.36
12:5	0.3479	0.08	68.7±0.02	430.38
12:8	0.3424	0.02	-	-
12:8	0.3422	0.05	41.8±0.02	478.38
12:8	0.3426	0.08	75.3±3.1	318.12
12:8	0.3425	0.15	65.7±2.3	197.09

Good solvent was used in this process to increase the amount of soluble drug and polymer in the organic solution and to uniformly disperse the Aerosil in this organic solution. When the amount of dichloromethane and the concentration of SDS in distilled water was fixed at 2.5ml and 0.08%, with increasing the amount of acetone from 3to 6ml, the recovery of micro particles was increased, but the bulk density and average particle size were decreased slightly Table 1.The reduction of the particle size of micro particles was probably due to the decrease in the viscosity of polymer solution with increasing the amount of good solvent. The pores and interstices of the micro particles, which were formed after good solvent being diffused out of droplets, were increased with increase the amount of acetone, leading to a decrease in the bulk density of micro particles. The increase of the recovery was probably due to the increasing dispersion of the emulsion droplets in poor solvent with an increase in the amount of acetone: the reduction of the conglutination of the polymer on equipment was observed in fact.

The emulsifier in poor solvent was also an important factor to affect the micro particles properties. Table 1 showed that the micro particles could not be obtained when the drug-polymer-Aerosil suspension was poured into poor solvent of low concentration of SDS (i.e.0.02%w/v).With an increase of SDS concentration, the recovery of the micro particle was decreased. However, the recovery reached a maximum and then decreased slightly. This is probably due to the decrease in particle size of micro particles with increasing the concentration of SDS.Some small micro particles passed though 60mesh sieve and could not be registered. These indicated that the SDS with a proper concentration made a contribution to the dispersed and stable formation of emulsion droplet in poor solvent. So, the presence of SDS was found to be indispensable for the formation of micro particles in this study.

Effect of agitation speed and temperature on recovery and micrometric properties of the micro particles

The agitation speed had evident influence on the particle size of the micro particles. As shown in Table2, increasing the agitation speed decreases the mean diameter of the micro particles. The increased mechanical shear force, produced by increasing the agitation speed, divided the suspension of drug, polymer, and aerosil into small droplets rapidly. On the other hand, the agitation speed had no detectable influence on the recover and bulk density of the micro particles.

Table 2: It shows the effect of agitation speed and temperature on recovery and micrometric properties of the micro particle.

Agitation Speed (rpm)	Temperature (C°)	Bulk density	Incorporation Efficiency (%)	D50 (µm)
400	30	0.31±0.02	68.4±0.02	340.43
500	30	0.30±0.01	73.7±0.01	165.34
700	30	0.28±0.01	77.3±0.01	134.16
700	08	0.29±0.01	69.4±0.02	332.26
700	20	0.27±0.02	71.8±0.01	164.36
700	32	0.25±0.01	63.5±0.01	226.72
700	38	0.21±0.02	51.3±0.02	326.37
500	32	0.22±0.01	56.1±0.02	212.45
400	38	0.25±0.02	48.6±0.02	311.26

As shown in Table 2, the recovery and bulk density of micro particles is decreased with increasing the temperature, but the temperature has no obvious influence on the particle size. It was found in this test that the conglutination of polymer on the equipment was increased with increasing the temperature, which led to a decrease in recovery of micro particles. The bulk density of micro particles was reduced slightly probably due to swelling of the droplets with increasing the temperature of the system, resulting in the formation of more pores and interstices in droplets after the diffusion of organic solvent out of the droplets. Swelling of Eudragit RSPO has also been observed by Kawashima[22] in preparation of micro particles using the emulsion-solvent diffusion method.

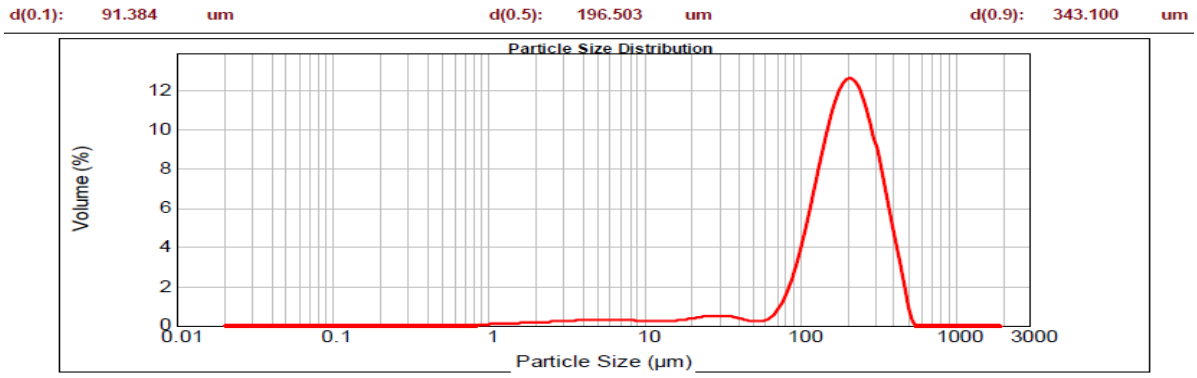
Table 3: It shows the effect of drug on drug loading and Incorporation efficiency of micro particles

Drug: EURSPO: Aerosil	Volume of dispersed phase	Viscosity	Particles Size (µm)	Drug loading (%)	Incorporation Efficiency (%)
1:2:3	11:9	0.3047	196.503	67±0.06	71.8±0.02
1:3:3	12:8	0.3426	319.096	78±0.12	79.3±0.01
1:4:3	14:6	0.3954	503.337	71±0.22	70.6±0.01

Drug loading and incorporation efficiency of micro particles

Table 3 indicates the content of aceclofenac in micro particles and also drug loss. As seen in this table, micro particle with high drug loading were obtained. Incorporation efficiency was high since it always exceeded 79%.As increasing the ratio of drug to excipients; the drug loading of micro particles was increased. The high content of aceclofenac in micro particles was believed to be due to the poor solubility that the present method was suitable for the preparation of micro particles of a poorly water-soluble drug, such as aceclofenac. The particle size distribution grape obtained from Malvern particle sizer (U.K) shows a sharp and steep peak, indicating that the range of particle size distribution of uniform and narrow (Fig 4.a,b, c.).The micro particles were found to be discrete, free flowing, spherical, smooth and were of the matrix type. The micro particles were with very narrow size range (196µm to 503µm).

a)



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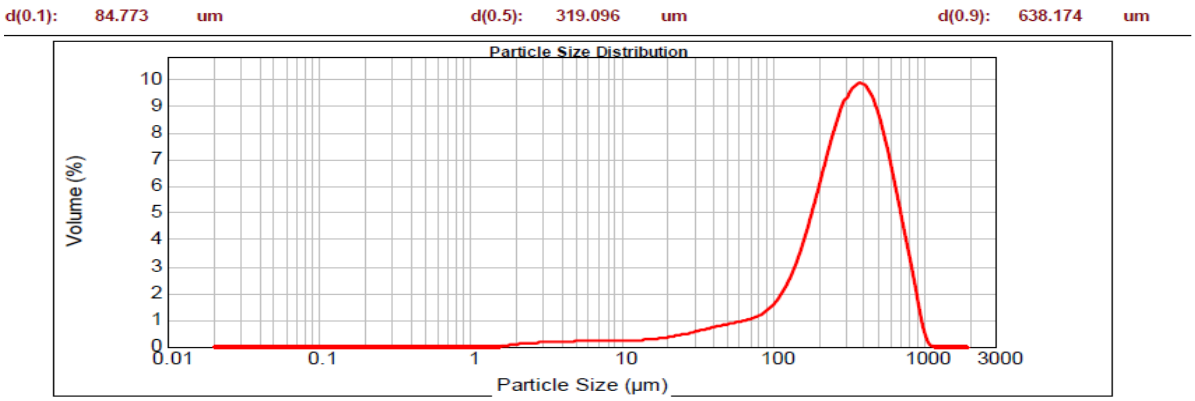

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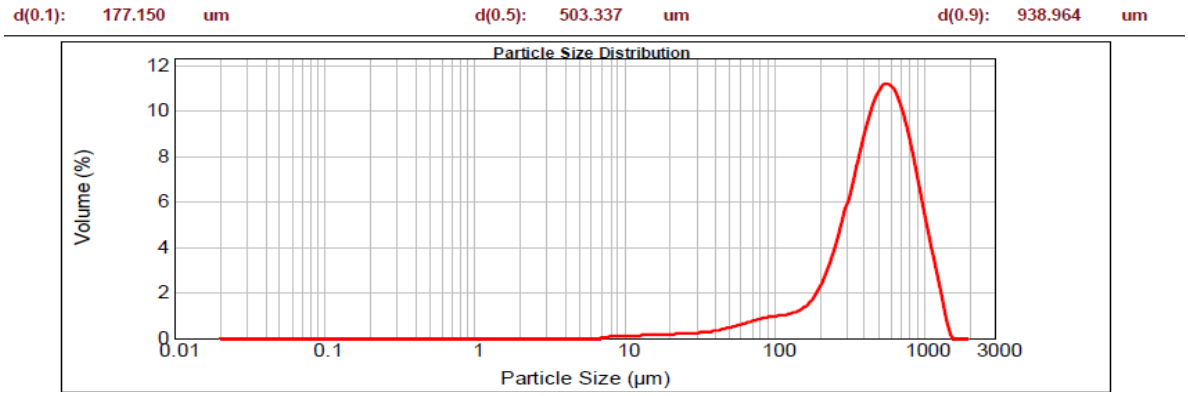

Fig. 4: It shows the particle size (µm) volume (%) distribution curve of micro particle. (a)Aceclofenac: EuRSPO: Aerosil (1:2:3), (b) Aceclofenac: EuRSPO: Aerosil (1:3:3), (c) Aceclofenac: EuRSPO: Aerosil (1:4:3) Measured in a Malvern particle

Control of drug-release behavior of micro particles

The release rate of aceclofenac from the micro particles could be modulated with adjusting the ratio of Eu RSPO to aerosil in the formulation. The influence of Eu RSPO on the release rate of aceclofenac was shown in Fig 5, when the ratio of the amount of drug to Aerosil was fixed at 1:3, increasing the amount of Eu RSPO resulted in a marked decrease in drug release. It was evident that Eu RSPO was efficient retarding agent to control the drug release rate.

When the ratio of the amount of drug to Eu RSPO in the formulation was fixed at 1:3, the release rate of aceclofenac from micro particles was increased with increasing amount of aerosil in formulation Fig 6.

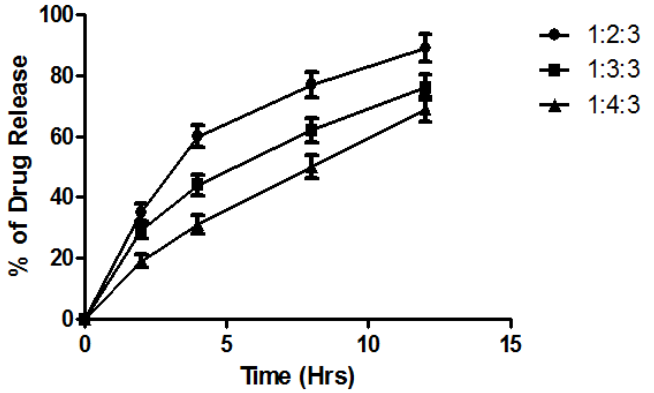

Fig. 5: It shows the effect of different ratio of Eu RSPO (Ac: EuRSPO: Aerosil, 1:2:3, 1:3:3, 1:4:3) on the release profiles.

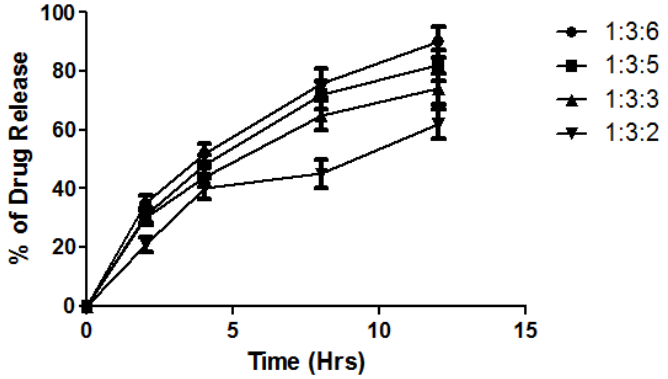

Fig. 6: Effect of different dispersion carrior on release profile of extended release

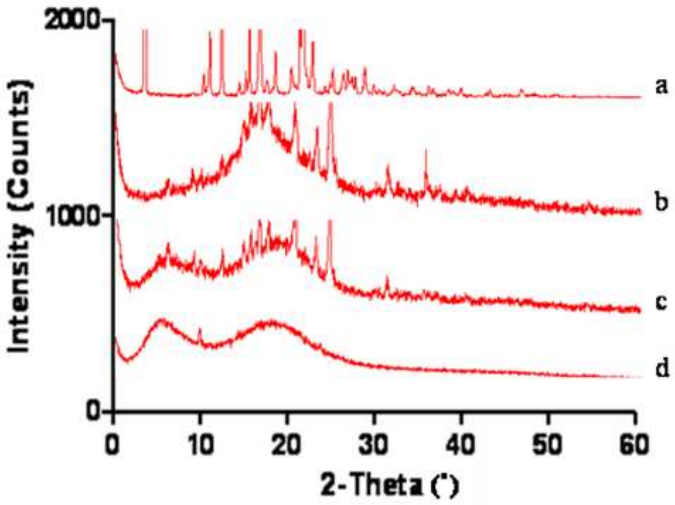

Fig. 7: It shows the X-ray powders diffractograms of aceclofenac, physical mixture.

a. Pure crystals of Aceclofenac, b.Aceclofenac: Eu RSPO: Aerosil (1:3:2), c. Aceclofenac: Eu RSPO: Aerosil (1:3:3), d. Aceclofenac: Eu RSPO: Aerosil (1:3:5).

Micro particles. (Aceclofenac: Eudragit: Aerosil - 1:3:6, 1:3:5, 1:3:3, 1:3:2)

As shown Fig 6 the release rate of micro particle of Aceclofenac: Eudragit RSPO: Aerosil 1:3:3 was much faster than that of Aceclofenac: Eu RSPO: Aerosil 1:3:2.And there were relatively minor increase in the drug-release rate when the ratio of the amount of Aerosil to aceclofenac was increased from 3:1 to 6:1.These results could be explained from X-ray power diffraction patterns of micro particles Fig 7.

As can be seen in Fig.7, the crystalline peaks of aceclofenac in micro particles disappeared gradually the ratio of Aerosil to aceclofenac in formulation. When the ratio of aceclofenac: Eu RSPO: Aerosil was 1:3:5, no crystalline peaks of aceclofenac was found in the microparticles, though the crystalline peaks were observed in the physical mixtures of the drug and excipients with the same formulation. Some small crystalline peaks of aceclofenac, however, could still be found in micro particles at the ratio of aceclofenac: Eu RSPO: Aerosil 1:3:2.These indicated that aceclofenac had been disordered in micro particles at the ratio of the amount of Aerosil to drug 3:1,suggesting that aceclofenac had been dispersed at this ratio, so as amorphous state.

Drug loading and incorporation efficiency of micro particles

Table 3 indicates the content of aceclofenac in micro particles and also drug loss. As seen in this table, micro particle with high drug loading were obtained. Incorporation efficiency was high since it

always exceeded 79%.As increasing the ratio of drug to excipients; the drug loading of micro particles was increased. The high content of aceclofenac in micro particles was believed to be due to the poor solubility that the present method was suitable for the preparation of micro particles of a poorly water-soluble drug, such as aceclofenac. The particle size distribution grape obtained from Malvern particle sizer (U.K) shows a sharp and steep peak, indicating that the range of particle size distribution of uniform and narrow (Fig 4.a,b, c.).The micro particles were found to be discrete, free flowing, spherical, smooth and were of the matrix type. The micro particles were with very narrow size range (196µm to 503µm).

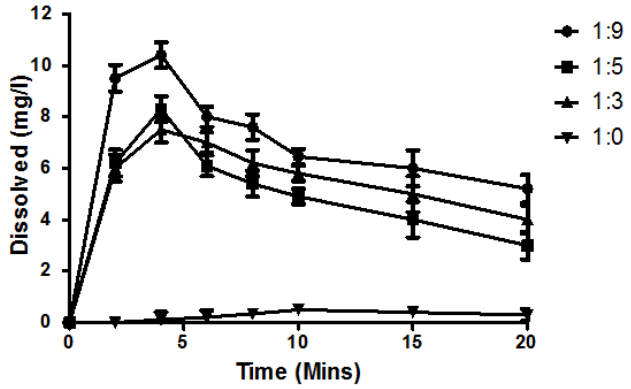

Fig. 8: It shows the dissolution profile of aceclofenac in distilled water (Ac: Aerosil, 1:9, 1:5, 1:3, 1:0)

As a dispersing carrier, Aerosil could improve the apparent solubility and dissolution rate of aceclofenac effectively. It was supported by the comparison test of dissolution rate of original aceclofenac powder and aceclofenac solvent deposition system Fig 8. This solvent deposition system was a solid preparation in which aceclofenac was deposited from a mixed solution of dichloromethane and acetone on the surface of aerosil. This step was done by simple evaporation of the organic solvent used for distribution of drug onto the Aerosil. The method of preparation of solvent deposition system has been described in detail in previous paper [23, 24]. The dissolution rate tests were carried out in distilled water in order to estimate other factors such as surfactant influencing on dissolution rate of the drug.

Finally proven that role of aerosil, as shown in Fig 8. Aceclofenac original powder has very low apparent solubility in distilled water. The dissolution rate of aceclofenac, however, was improved markedly after the drug was deposited on aerosil and was also increased with increasing the ratio of aerosil to drug.

Stability of Micro Particles

The stability data of extended-release Aceclofenac micro particles having a solid dispersion structure are presented in Table 4. The results obtained in the stability test showed that the content and release rate of Aceclofenac from sustained-release micro particles stored at a temperature of 40^{0}C and a relative humidity of 75% was unchanged during 3 months of accelerating condition storage. It was indicated that solid dispersion incorporated in microspheres was stable, probably due to the fact that the stable excipients such as, Eu RSPO, EC and Aerosil were employed in the preparation process of micro particles; another reason was that a relatively large ratio of the amount of excipients to drug was formulated in this micro particles, which contributed towards protecting the dispersion state of the drug.

Table 4: It shows the stability of Extended-release Aceclofenac micro particles under accelerating condition (n=6, x ± SD)

Time (month)	Content (%) (1:3:3)	Percent released (%) 1h	3h	6h	9h	12h
0	99.65±0.53	24.27±1.01	36.21±1.26	53.22±1.33	72.45±1.34	81.65±0.27
1	99.73±0.23	19.68±1.33	35.13±1.22	54.07±1.54	72.50±1.03	82.05±1.02
3	99.94±0.22	27.30±0.79	36.84±0.68	52.39±0.56	71.30±0.55	79.58±0.94
6	99.67±0.32	20.86±1.23	37.53±1.55	54.44±2.05	73.32±1.87	80.68±1.47

CONCLUSION

Extended-release Aceclofenac micro particles with Eu RSPO and Aerosil was prepared using an emulsion solvent evaporation technique were prepared successfully in one step using a spherical crystallization technique by combination of the formulation of micro particle and the solvent deposition system in one step. The preparation process was simple, reliable and inexpensive; the resultant micro particles have the desired micromeritic properties. The release profiles of the micro particles were modulated with adjusting the ratio of the retarding agent to the dispersing carrier. The relatively high recovery and incorporation efficiency of micro particles also showed an advantage over the other conventional method of preparing micro particles. The markedly improved release characteristics of Aceclofenac micro particles indicated that the present method was an efficient combination of the formulation. And it was indicated that the present method was suitable for preparing the extended-release micro particles for poorly water-soluble drug.

The formulation phase is a critical phase in establishing the properties of CDs (central composite designs) that will allow suitable risk assessment for development. Typically it begins during the lead optimization phase, continues through predomination, and on into the early phases over development. Decisions made on the information generated during this phase can have a profound effect on the subsequent development of those products.

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