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Characterization and Release Kinetics of Microspheres and Tableted Microspheres of Diclofenac Sodium

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ABSTRACT

This study reports the properties of tableted microparticles based ethylcellulose blend polymers as the controlled release system for diclofenac sodium (DS). Ethylcelulose blend microparticles are prepared through a solvent evaporation process which is a widely used microencapsulation technique in the pharmaceutical industry. The microspheres were characterized for their particle size and distribution, tapped density and encapsulation efficiency. Smaller sized particles with a narrow size distribution were produced with Ethylcellulose .The blend microparticles thus prepared were compressed into tablets using the directly compressible excipients. A cross-sectional view of the tablet reveals the presence of nearly spherical shaped particles in the tablet, suggesting that the system chosen is ideal for tableting. Drug release from compressed tablets was always faster than from uncompressed microspheres, but useful sustained-release characteristics were retained. Dissolution tests of formulations of the tableted microspheres showed increased release rate constants and decreased 50 per cent dissolution times compared to microspheres that had not been compressed. This result indicated that rupture of some of the microspheres had occurred. The drug release rate increased at higher compression pressures due to the rupture of a greater proportion of microspheres. Generally, the least compression pressure that gives tablets with acceptable properties is preferred.

Keywords: Microparticles, Controlled release, Diclofenac sodium, Tableted microparticles and Solvent evaporation.

INTRODUCTION

Diclofenac sodium (DS) is a nonsteroidal drug having a potent antiinflammatory, analgesic, and antipyretic effect. It is an inhibitor of prostaglandin

synthetase. It is used for the relief of pain and inflammation in conditions, such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, and those following some surgical procedures. It has an unpleasant taste and causes gastric irritation. DS is mainly absorbed from the GIT.[1] It is a phenylacetic acid derivative with a pKa value of 4.0. It is practically insoluble in acidic solutions but dissolves in intestinal fluid and water. It is generally known that DS gets into the blood within 30 min and reaches the maximum blood concentration (Cmax) within 1.5–2.5 h following oral administration of an enteric coated tablet. The maximum average concentration in the blood is between 0.7 and 1.5mgL_1. The oral bioavailability is around 60% with an excretion half-life between 1.1 and 1.8 h.[2]

Ethylcellulose (EC) is a polymer of β-anhydro-glucose building blocks joined together by acetal bonding. It is generally considered as a nontoxic, biocompatible and non-biodegradable polymer. EC coated microparticles have also demonstrated their capability to absorb pressure and therefore save the coating from fracture during tablet manufacturing process. This process involves conversion of multi-unit system into a single unit dosage form by compression. This single unit system disintegrates slowly into sub-units when exposed to dissolution process.[3, 4]

Controlled release multiple-unit oral dosage forms are effective in achieving optimal therapy with drugs that have a narrow therapeutic range of blood concentration or that eliminate rapidly and reduce the risk of gastric irritation at one particular site because of the uniform distribution of the drug throughout the GIT. Polymeric microparticles are widely studied carriers for the controlled release application of drugs. Encapsulation of drugs into polymeric matrix can be achieved by techniques, such as solvent evaporation , coacervation, spray drying,[5] etc. Tableting of polymeric microparticles would result in controlled release of the drug. After tableting of microparticles, the particles may remain intact within the tablet without undergoing merging or rupturing and, hence, drug release will take place from the individual microparticles; if not, the microparticles may merge or rupture to become bigger compacts. In such cases, the release will occur from compacts in the tablet formulation. Ideally, the drug release should occur from the individual particles, which should not be affected by the compression process. However, excipients used in tableting should provide a sufficient cushioning effect to withstand the compression force and, thereby, prevent the merging or rupturing of the microparticles. In particular, ethylcellulose based microparticles have gained much more attention in developing controlled release microparticulate systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[6] Controlled-release characteristics of microparticles reduce the need for frequent administrations and enhance patient compliance by maintaining in drug levels in the therapeutic range.[7] Thus, oral controlled release multiple-unit drug delivery systems, such as microparticles, beads, and pellets have gained widespread importance due to their numerous advantages over conventional single-unit dosage forms. Once the tablet or capsule containing multiple units disintegrates, particles spread uniformly throughout the gastrointestinal tract (GIT). This will avoid the release of the drug at one particular site, thus avoiding the risk of toxicity caused by the locally restrained tablet within the GIT. A uniform distribution of multiple units in GIT results in more

reproducible absorption and will reduce the risk of local irritations, compared to single-unit systems.[8] Multiple units can be filled into hard gelatin capsules or they can be compressed into tablets. However, the formulation of multiple units into tablets has the advantage of preventing tampering, as in the case of capsules, but the merger of these multiple systems during compression can produce variations in the controlled release of the drug.

MATERIALS AND METHODS

Material

Diclofenac Sodium was obtained as a gift sample from Cris Pharma India. Ltd. Selaque, Dehradun. Lactose, Microcrystalline cellulose, Talc, Magnesium stearate, PVP K-30 was supplied as gifts by Central Drug House Pvt. Ltd., New Delhi, India.

Methods

Preparation of Microspheres: Solvent Evoporation Method

Diclofenac Sodium microspheres were prepared by different formulation. Desired amount of Diclofenac Sodium was dissolved in distilled water. Polymer (ethyl cellulose) was dissolved separately in dichloromethane. Then the aqueous drug solution was gradually added to above prepared polymeric solution with constant stirring at 600 rpm, stirring was continued for few minutes. Then the primary emulsion was added to PVA solution containing 2% span 80 stirring was continued up to 2 hrs at a temperature of 60^{o}C in a 250 ml glass beaker. After 2 hours of stirring, hard, spherical microspheres were obtained. Microspheres were then washed three times with petroleum ether and vacuum-dried to obtain free flowing microspheres (figure 1).

Surface Morphology & Measurment of particle Size

The surface morphology of drug-loaded microparticles, tableted microparticles, and fractured part of tableted microparticles were examined by means of a Zeiss, Evo 40(India) scanning electron microscope.[9] Particle Size also determined by scanning electron microscope.

Physical Evaluation of microparticles

Density, compressibility index, hausnner's ratio and angle of repose were calculated according to the previous works.[10]

Assay of Diclofenac sodium

An accurately weighed quantity of microparticles and tableted microparticles from each batch was treated as described previously[12] then analyzed spectrophotometrically at 276 nm, against its standard solution under the same conditions. The entrapment efficiency was determined by the following equation:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Amount of drug found in microparticles}}{\text{Amount of drug used for microencapsulation}} \times 100$$

The percentage production yield of the produced microparticles was calculated for each batch by dividing the weight of microparticles (M) by the total expected weight of DS and EC[13,14] (Mt):

$$\text{Production yield (\%)} = M/M\,t \times 100$$

Each determination was performed in triplicate.

Physical Evaluation of Tableted microsphere

The tableted microparticles were evaluated with respect to weight variation, tablet hardness, friability and thickness.[11] Disintegration tests were performed in 0.1N HCl (pH 1.2) at 37^{o}C.

Drug Content of Tableted Microparticles

Each tablet was crushed into powder in a mortar and then the powder was soaked in 100mL of phosphate buffer solution (pH 6.8) for 24 h followed by sonication for 5 min. The solution was passed through a 0.2 mm membrane filter (Millipore) and then the drug content was determined by measuring the absorbance at 276nm using a UV spectrophotometer (Elico SL 210). Experiments were repeated in triplicate in an identical manner.

In vitro Drug Release

Drug release from the pure DS tablet and tableted microparticles was studied by using a dissolution tester (Electro lab) at a stirring speed of 100 rpm. Three tablets from each batch were tested using 900mL of dissolution medium (phosphate buffer, pH 7.4), maintained at 37°C. An aliquot of the release medium (5mL) was withdrawn through a sampling syringe attached with 0.2 mm filtrate predetermined time intervals (0.5, 1, 2, 3, 4, 5, and 6 h) and an equivalent amount of fresh dissolution medium, which was prewarmed at 37°C, was replaced. Collected samples were then analyzed for DS content by measuring the absorbance at 276nm using a UV spectrophotometer. In vitro release studies were performed in triplicates in an identical manner.[15]

Model analysis and Statistics

The methods which were employed to compare drug release profiles can be classified into two categories: model dependent and model independent approaches. Model-dependent approaches include Zero Order, First Order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas Kinetic Model and were employed to analyze dissolution data in this study.[16]

RESULTS & DISCUSSION

Diclofenac Sodium microspheres were prepared by solvent evaporation technique with different polymeric concentrations of ethyl cellulose. Effect of different concentrations of EC Diclofenac sodium microspheres were successfully examined with respect to microparticles, drug loading efficiency and release kinetics.

Surface Morphology & Measurement of particle Size

In DS microparticles, exhibited a smooth surface (Figure 2). When compressed, the microparticles were still intact and maintained their shape. The particle size of DS microparticles was found to be in the size range of 25µm by SEM. A scanning electron micrograph of the cross section of the tableted microparticles is given in Fig no 3, from which it can be seen that, within the tablets, microparticles are present as individual particles without compacting during compression. Figure 4 shows tableted microsphere.

Since this is an ideal requirement for producing the tableted microparticles, the procedure used in this research is suitable for tableting.

Physical Evaluation of Tablets

As given in table 1, there was a decrease in bulk density with the increase in polymer concentration. Such relationship between bulk density and polymer concentration has been reported previously. Compressibility index (less than 15%) indicated fine flow properties. Hausner's ratio (volume before taping/volume after taping), for all formulations, was below 1.29 again indicating free flow of all formulations of microparticles. Similarly angle of repose for all formulations were below 30° indicating once again free flowing nature of microparticles.

Physical Evaluation of Tableted microsphere

It was found that the encapsulation efficiency is influenced by core to wall ratio. With increasing EC ratio, more particles of Diclofenac Sodium are coated which leads to a higher encapsulation efficiency [17, 18] (table 2). An increase in EC concentration caused a slight increase in production yield of microparticles. The results of the hardness, thickness, and disintegration time of tableted microparticles are presented in Table 3. The DS-loaded microparticles thus prepared were successfully compressed into tablets. The hardness of various formulations of tableted microparticles was in the range of 5–5.9 kg cm^2. The thickness and disintegration time of all the blend microparticulate tablets were between and 17 and 26 min, respectively. The results of the assay of the tableted microparticles indicated uniformity in drug content in the tablets since the drug content was found to vary between 93.4 and 97.3%.

In vitro Drug Release

Initial part that indicates fast drug release in the start (desired for immediate therapeutic effect) and then tentatively a zero order plot segment that indicates a slow drug release (for prolonged effect). This result can be supported by an argument that it is the drug particles attached on the external surface of microparticles, responsible for initial rapid release and then subsequently slow drug release from the core of microparticles by diffusion. It was found that the formulations follow the Zero order kinetics and exhibits best correlation by the Higuchi equation proving that the release is by diffusion mechanism. Moreover, Korsemeyer- Peppas model showed anomalous mode (diffusion plus erosion) of drug release. The value of n could be used to characterize different release mechanism. The value of n for F1 to F3 was found between 0.667-0.859 thus the formulations indicate that the release approximates non-Fickian diffusion mechanism (table 4).

The microparticles thus prepared were compressed into tablets. The release rate of the DS from conventional tablets was rapid and more than 95% of the drug was released within 30 min of the dissolution study (see Figure 5). Tableted microparticles exhibited controlled release of the drug. However, the cumulative amount of drug release was affected by the ratio between Drug and polymer. For instance, tableted microparticles based on 1: 3 (drug to polymer) ratios exhibited lower cumulative amount of drug release when compared to 1: 1 & 1:2 ratios. More specifically, tableted microparticles based on 1: 3 ratios were found to be better formulations since they exhibited effective sustained drug release, compared to other formulations.

CONCLUSION

This study elaborated that the solvent evaporation technique is an appropriate method to microencapsulate Diclofenac sodiume into the ethylcellulose coats. It could be concluded that the variation observed in entrapment efficiency, mean particle size and the drug release behavior among the formulations are the result of the drug polymer ratio employed. These results may suggest the potential application of ethylcellulose microparticles as a suitable sustained release drug delivery system. Therefore, by using ethylcellulose it is possible to formulate a single-unit, sustained-release oral dosage form of Diclofenac sodium twice in every 24 hrs.

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Table 1. Rheological Properties of Microparticles

Formulations	Bulk density (g/ml)	Taped density (g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose
F1	0.31	0.24	10	1.14	21.82°
F2	0.28	0.32	12	1.02	24.14°
F3	0.22	0.34	11	1.28	28.35°

Table 2. Evaluation of physical characteristics of Diclofenac sodium microparticles

Formulations	DS:EC ratio	Entrapment efficiency (%)	Production Yield (%)
F1	1:1	94	96.24
F2	1:2	96	97.22
F3	1:3	97	97.89

Table 3. Evaluation of physical Properties of Diclofenac sodium microparticles

Formulations	Drug content of tablets (%)	Hardness (kgcm_2)	Thickness (mm)	Disintegration Time (min)
F1	93.8	5.4	3.84	17
F2	95.5	5.6	3.76	21
F3	97.7	5.9	3.65	26

Table 4. Model fitting release profile of Formulations F1 to F3

Formulations	Regression Coefficient			Slope (n) Value
Code	Zero Order	First Order	Higuchi	Korsmeyer Peppas
F1	0.981	0.969	0.969	0.667
F2	0.988	0.982	0.938	0.760
F3	0.991	0.968	0.907	0.859

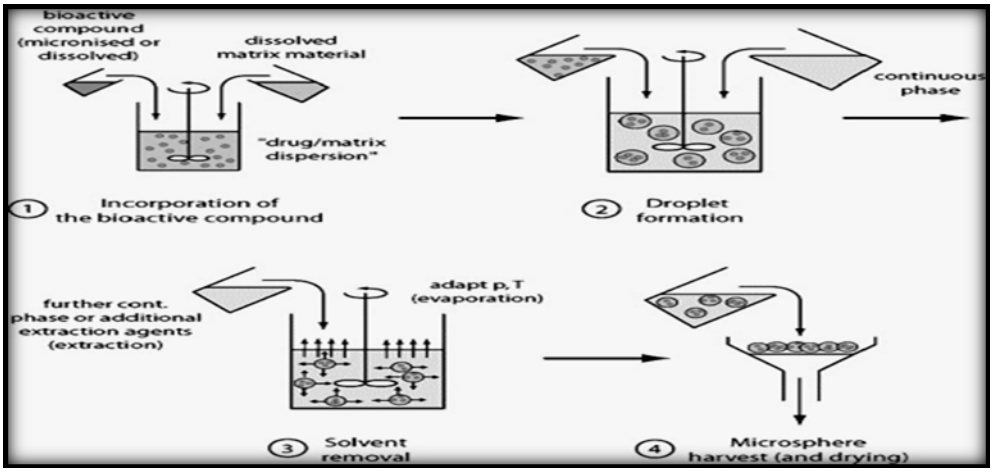

Figure.1. **Solvent Evoporation Technique**

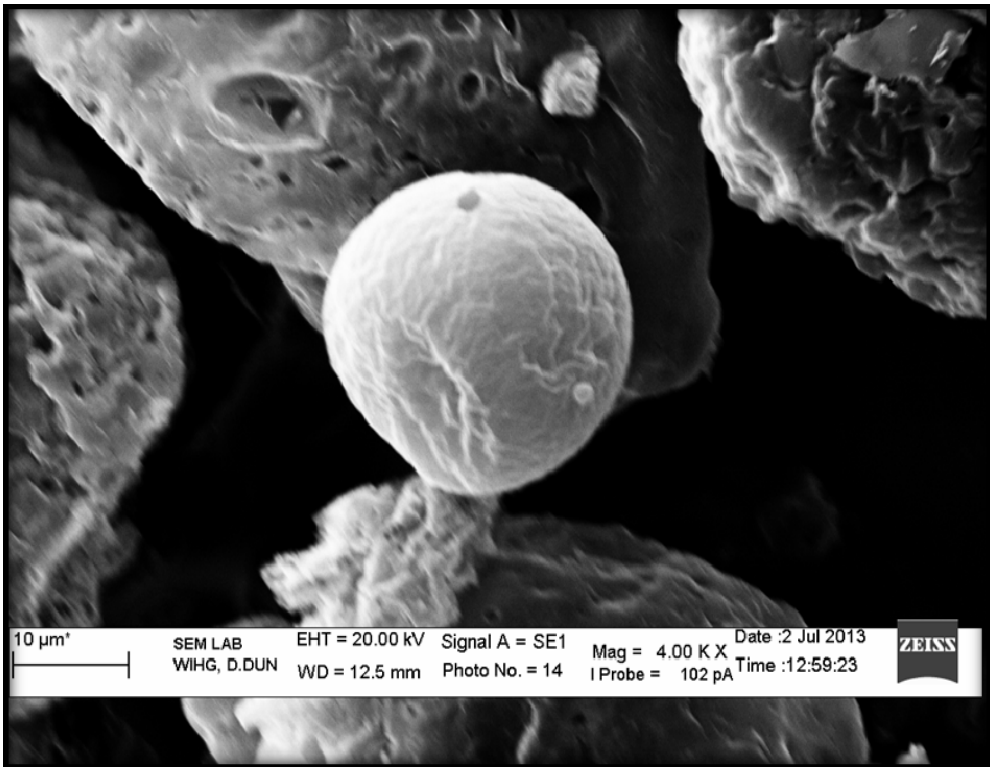

Figure.2. **Scanning electron micrograph Drug loaded microparticle**

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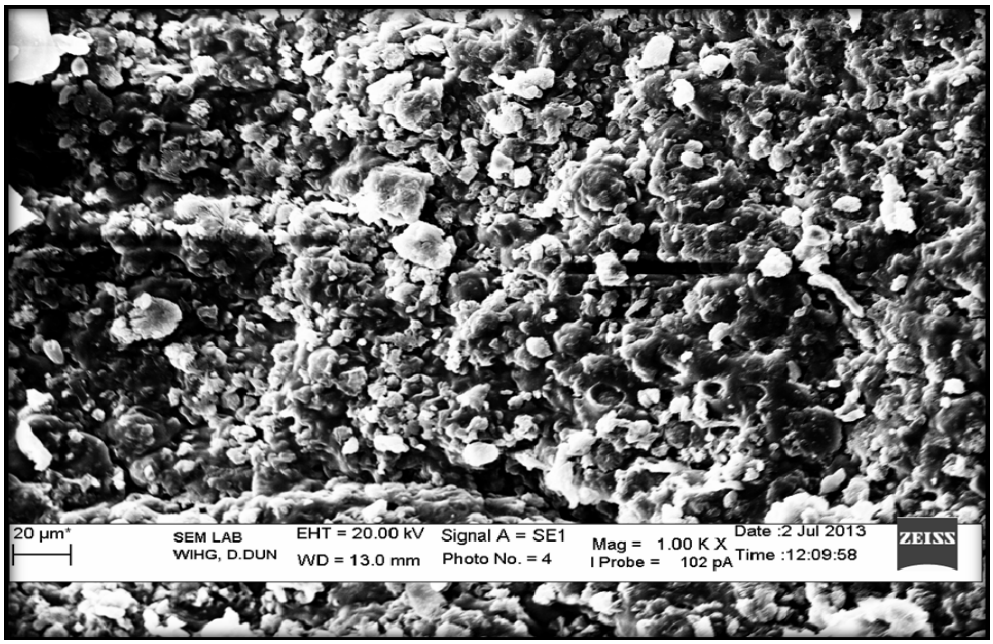

Figure.3. **Scanning electron micrograph of fractured part of tableted microparticles**

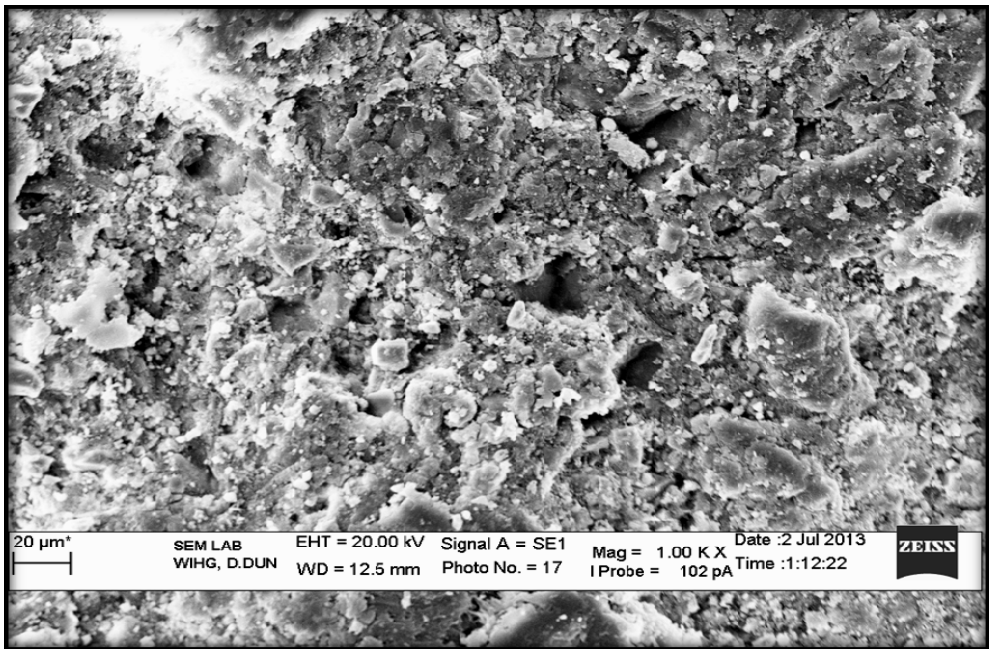

Figure.4. **Scanning electron micrograph of tableted microparticles.**

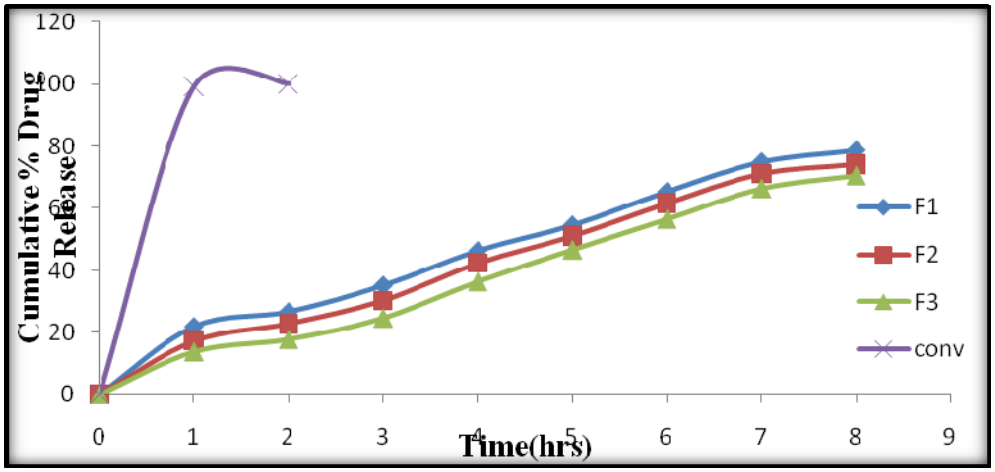

Figure.5. **Cumulative amount of DS release (% release) with time from various formulations of tableted microparticles along and tablet containing DS alone (conventional tablet)**