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Research Article

METFORMIN HYDROCHLORIDE MICROPARTICLES FOR ORAL CONTROLLED RELEASE: EFFECT OF FORMULATION VARIABLES*

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ABSTRACT

Objectives: The aim of the present study was to evaluate effects of various polymers on the release of a water soluble drug by using spray drying technique of microencapsulation.

Methods: Spray drying is a single step technique, less time is required and loading efficiency is not affected by the nature of the drug whether hydrophilic or hydrophobic. Eudragit RS 30D, RL 30D and Ethylcellulose (Surelease) were chosen as rate controlling polymers. Various drug to polymer ratios used were 1:1, 1:2, 1:3, 1:5, 1:7, 1:9 and 1:11. The microparticles were characterized by encapsulation efficiency, particle size, powder x-ray diffraction, DSC, scanning electron microscopy, and in-vitro drug release.

Results: No drug excipient interaction was observed in DSC studies. The maximum control of the drug release was observed at the lowest drug to polymer ration i.e. 1:11. Since the drug is freely soluble in water it was difficult to control its release. Among the three polymeric dispersions used, Eudragit RS 30D exhibited better control on the release of drugs. Powder X-ray diffraction studies revealed that there is no conversion of the drug from its original crystalline state to amorphous state after the spray drying process.

Conclusion: Spray drying can be used as a method for the formulation of controlled release drug delivery systems. Eudragit RS 30D showed better control over drug release, this may be due to less penetration of water within the microparticles.

Keywords: Spray drying, Metformin Hydrochloride, Polymeric dispersions, Microparticles, Controlled-release, Eudragit.

INTRODUCTION

Administration of the conventional dosage forms does not usually provide rate-controlled release or target specificity. It is observed in many cases, the conventional drug delivery provides sharp increases of drug concentration at potentially toxic levels. Following a relatively short period at the therapeutic level, drug concentration eventually drops off until re-administration. Today new methods of drug delivery are possible: desired drug release can be provided by rate-controlling membranes.

Administration of a drug by microspheres has been studied from last many years. Microspheres as a drug carrier has many advantages which include, they can be injected as well as ingested, can be modified for desired drug release, organ targeted drug delivery is possible, avoids variance of gastric emptying and different transit rates, releases the drug in a more predictable way, rapid and easy to scale up [1] [2] [3] [4].

Metformin is a new generation biguanide. Its action involves increased peripheral tissue utilization of glucose and decrease hepatic glucose production. Metformin acts by decreasing hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake. Because of its shorter and variable biological half-life of 1.5–4.5 hrs, it should be repeated administered (250 mg twice or thrice a day) to maintain effective plasma concentration [5] [6].

Metformin hydrochloride being a water soluble drug, it is difficult to control the release of water soluble drugs over the time period desirable to achieve better plasma concentration using spray-drying method for the preparation of microparticles [7].

Spray drying has gained more importance as a method of microencapsulation. This method has already been used to prepare microparticles with polyesters, polymethacrylates, cellulose derivatives and biopolymers containing both hydrophilic and lipophilic drugs and macromolecules. The major advantages over solvent evaporation techniques are the one-step process, the easiness to control and scale up, and the possibility of being free of organic solvents.

When used with organic solvents, the amount of residual solvent in particles is often lower than that reached with emulsification-solvent removal technique. It is less dependent on the solubility parameters of the drug and the polymer.

Spray-drying technique has inconveniences related to processing variables that must be well controlled to avoid difficulties such as low yields, sticking, or high moisture content. These are often encountered with laboratory scale spray-dryers.

It was found that aqueous based systems have more advantages compared to the systems based on the organic solvents (spray-drying technique). The use of aqueous systems is becoming increasingly popular, since organic solvents incur risks of product contamination, toxicity, fire and explosion hazards [8] [9].

G. Di Colo et. al. Formulated pH-controlled peroral delivery of Metformin [5], Lian-Dong Hu et. al. Prepared sustained-release Metformin hydrochloride pellets [10].

Gastrointestinal absorption of Metformin is not complete with an absolute bioavailability of 40–60% (under fasting conditions) this is combined with rapid elimination, out of the total dose administered 20–30% of an oral dose is recovered in feces. Side effects and the need for twice to three times a day administration when larger doses are required can also reduce patient compliance. Administration of a sustained-release, once-a-day Metformin hydrochloride dosage form could reduce the dosing frequency and improve patient compliance [10]. P.K. Choudhury et. al. Prepared Metformin hydrochloride microspheres and evaluated the effects of polymer related parameters, emulsification method was used in this study [11]. M. Kar et. al. Formulated Metformin Hydrochloride microspheres, polymer used was Ethylcellulose. Microspheres were prepared by the double emulsion solvent diffusion method [12].

MATERIALS AND METHODS

Materials

Metformin Hydrochloride (USV Ltd. Mumbai, India), Methacrylic acid co-polymers (Eudragit® RS 30D and RL 30D) (Evonik-Degussa, Mumbai, India), Ethylcellulose aqueous dispersion (Surelease®) (Colorcon Asia, Goa, India), Colloidal silicon dioxide (Pharma 200®) (Evonik-Degussa, Mumbai, India), talc (Wockhardt Ltd, Aurangabad, India). All other excipients and reagents used were of analytical reagent grade.

Methods

Microencapsulation process

As mentioned previously microparticles were prepared by spray-drying technique. In the process three polymeric dispersions namely Eudragit RS 30D, Eudragit RL 30D and Ethylcellulose (Surelease) were selected as a rate controlling polymers. Inlet temperature was maintained at 125±2^{0}C, Outlet temperature 80 ± 5^{0}C, Feed rate 20%, Aspirator 50%, Feed concentration used was 7% W/V, a two fluid (0.7mm diameter) atomizer was used and the atomization pressure used was1 bar. All the batches were processed through Labultima LU-22 spray-drier.

Metformin Hydrochloride was completely dissolved in distilled water by using a mechanical stirrer at 400rpm, the required volume of the polymers is then measured and then this is dispersed in drug solution. Colloidal silicone dioxide and talc was then weighed which is then added into the previously made solution. Various Drug : Polymer ratios used were 1:1, 1:2, 1:3, 1:5, 1:7, 1:9, 1:11. Microparticles were then collected and kept in desiccators until used further.

Percentage yield

Following formulas were used for calculation of % Yield

$$\text{Yield \%} = \frac{\text{Wt. in gms of the product obtained in collecting vessel} \times 100}{\text{Feed concentration in gms.}}$$

Encapsulation efficiency [7]

Samples of the microparticles were weighed and then completely dispersed in distilled water, sonicated using bath sonicator for 30 min. For extraction and complete solubilization of Metformin hydrochloride. Then the volume was made up with distilled water. Then the samples were passed through 0.45µm syringe-filter and after dilution the concentration was determined by UV spectroscopy (Jasco V 530, Japan) at λ max of 274 nm. All the determinations were performed in triplicate and final results were expressed as percentage of the corresponding Metformin hydrochloride amount added initially. Following formula was used for calculation of encapsulation efficiency.

$$\text{Encapsulation Efficiency \%} = \frac{\text{Practical drug content} \times 100}{\text{Theoretical drug content}}$$

Particle size analysis

Particle size analysis was performed by microscopy method with imaging facility by using advanced Motic digital microscope model BA210. Total 200 particles were measured for each formulation and the average particle size is calculated.

Differential scanning calorimetry (DSC)

Physical mixtures of drug, polymer and other excipients were prepared by suing the same proportions as used in the all the formulation batches processed. The polymeric dispersions were dried in Petri dishes for three days at room temperature. A film of the polymers was obtained[13] which was the crushed using mortar and pestle. In the case of Surelease (Ethylcellulose), the formed film was so elastic that it was difficult to crush, that's why Ethylcellulose was used in the already dried state. The physical mixtures were examined by using differential scanning calorimeter (Schimadzu, DCS-50 cell Japan) using the pans with lid with about 1 mg of sample. Weighed samples were sealed in an aluminum pan with a lid. Samples were heated between 25^{0}C to 400^{0}C at the interval of 5^{0}C/min.

Powder X-ray diffraction

Metformin Hydrochloride and loaded microparticles were subjected to X-ray diffraction study.

In-vitro dissolution testing [14]

Dissolution study was carried out for pure drug and for all batches of microparticles. Phosphate buffer pH 6.8 was used as a dissolution medium.

Since the microparticles were very fine, a dialysis bag was used to carry out the dissolution testing. Microparticles equivalent to 50 mg of Metformin hydrochloride were weighed accurately, and then dispersed into the dialysis membrane (Molecular weight cut off was 12000 Daltons). Then the membrane was placed into the basket and rotated at 100rpm. Samples were withdrawn at the time interval of 1, 2, 3, 4, 6, 8, 12 and 24 hrs. The volume equivalent to sample withdrawn was replaced by dissolution medium to maintain the sink condition.

Scanning electron microscopy

The microspheres were coated with gold after fixing the samples in individual stubs. All samples were examined for surface morphology using a scanning electron microscope (Jeol JSM -6360 Scanning microscopy, Jeol, Japan) at 20 kv.

RESULTS AND DISCUSSION

Percentage Yield (% W/W)

Yield obtained in all the batches is observed to be low. As can be seen in the table No.1 maximum yield obtained was with formulation SF3 (Eudragit RS30D), which is 20.68 ± 0.88, and minimum yield obtained with formulation LF4 (Eudragit RL30D). The average yield obtained with formulations prepared by combining Metformin Hydrochloride and Eudragit RSPO is 15.96 ± 0.49, average yield obtained with formulations prepared by combining Metformin Hydrochloride and Eudragit RLPO is 11.34 ± 0.58 and average yield obtained with formulations prepared by combining Metformin Hydrochloride and Ethylcellulose (Surelease) is 08.51 ± 0.38. The average yield obtained with Ethylcellulose is low. The reason may be, during spray-drying process it was observed that most of the microparticles got adhered to the walls of the drying chamber. Adhesion to the cyclone walls was also observed and triboelectrification phenomenon i.e. electrostatic charging upon contact and friction between particles and spray dryer glass walls could explain, at least to some extent, the powder deposits [15]. Because of this very low quantity of the product get collected in the collecting vessel. It has been observed in the past that spray-drying has inconvenience which is related to the processing variables which must be well controlled to avoid problems like sticking of the product [16]. Two main reasons were quoted for low yield in spray drying 1) cyclone separator is unable to trap particles which are below 2µm size and let them pass into the outlet air. 2) inadequate process parameters which makes the particle adhere to the inside walls of the instrument [17].

Table 1: Yield in percentage of concentration total feed

Sr. No.	Formulation Code	D:P Ratio	Yield % (n=3)
1	SF 1	1:1	13.33 ± 0.54
2	SF 2	1:2	19.46 ± 0.69
3	SF 3	1:3	20.68 ± 0.88
4	SF 4	1:5	14.41 ± 0.07
5	SF 5	1:7	12.52± 0.08
6	SF 6	1:9	14.13± 0.55
7	SF 7	1:11	17.22± 0.64
8	LF 1	1:1	14.80 ± 0.45
9	LF 2	1:2	12.43 ± 1.20
10	LF 3	1:3	15.70 ± 0.82
11	LF 4	1:5	1.90 ± 0.560
12	LF 5	1:7	09.17± 0.15
13	LF 6	1:9	11.15± 0.24
14	LF 7	1:11	14.25± 0.68
15	CF 1	1:1	06.71 ±0.73
16	CF 2	1:2	11.09 ±0.23
17	CF 3	1:3	09.98 ±0.63
18	CF 4	1:5	09.88 ±0.29
19	CF 5	1:7	08.45± 0.07
20	CF 6	1:9	07.25± 0.15
21	CF 7	1:11	06.23± 0.56

Encapsulation Efficiency

Encapsulation efficiency obtained with all the batches is high. All the values are mentioned in Table 2. The maximum encapsulation efficiency obtained with formulation SF3 is 115.31 ± 2.48, and the minimum was obtained with formulation LF7 which is 101.22± 1.17. No variation is observed with the encapsulation efficiency with changing drug : polymer ratios. In all the formulations encapsulation efficiency is higher that 100%. These results are consistent with the findings of Nizar Al-Zoubi et. al. [8]. Higher encapsulation efficiencies were also reported in previous research works by various research groups [18] [19].

Table 2: Encapsulation efficiency of microparticles

Sr. No.	Formulation Code	D:P Ratio	Encapsulation efficiency (%) (n=3)
1	SF 1	1:1	112.84 ± 1.33
2	SF 2	1:2	113.95 ± 1.98
3	SF 3	1:3	115.31 ± 2.48
4	SF 4	1:5	103.12 ± 1.52
5	SF 5	1:7	107.44± 1.48
6	SF 6	1:9	105.24± 1.22
7	SF 7	1:11	103.12± 1.45
8	LF 1	1:1	105.56 ± 1.73
9	LF 2	1:2	107.68 ± 0.88
10	LF 3	1:3	110.06 ± 2.20
11	LF 4	1:5	108.31 ± 1.52
12	LF 5	1:7	108.24± 1.42
13	LF 6	1:9	104.14± 1.27
14	LF 7	1:11	101.22± 1.17
15	CF 1	1:1	108.49 ± 1.71
16	CF 2	1:2	108.29 ± 0.70
17	CF 3	1:3	105.78 ± 1.23
18	CF 4	1:5	107.69 ± 1.10
19	CF 5	1:7	102.23± 1.16
20	CF 6	1:9	105.05± 1.26
21	CF 7	1:11	104.12± 1.14

Particle size analysis

The average particle size is in the range of 4.39±0.85 to 6.77±2.24. Details can be seen in table no. 3 Particle size can also be confirmed from SEM images.

Table 3: Average particle size of all formulations

Sr. No.	Formulation Code	Average particle Size
1	SF 1	5.35±2.45
2	SF 2	6.04±2.25
3	SF 3	6.61±2.76
4	SF 4	6.00±2.43
5	SF 5	4.55±0.88
6	SF 6	5.78±2.50
7	SF 7	6.19±2.64
8	LF 1	5.18±2.00
9	LF 2	5.03±1.62
10	LF 3	4.99±1.72
11	LF 4	6.77±2.24
12	LF 5	4.39±0.85
13	LF 6	5.76±2.22
14	LF 7	5.78±2.03
15	CF 1	5.40±2.20
16	CF 2	5.00±3.13
17	CF 3	4.88±1.81
18	CF 4	4.68±2.50
19	CF 5	4.41±0.85
20	CF 6	4.86±3.14
21	CF 7	6.53±2.74

Differential scanning calorimetry (DSC)

DSC is one of the general methods to find out the physicochemical interaction between the drug and polymer in a formulation. DSC thermogram for pure drug, pure polymers, excipients and their physical mixture and various formulations were recorded and demonstrated in Fig. 2.

For Metformin hydrochloride a sharp endothermic peak was observed which begins at 228.30^{0}C and ends at 236.16^{0}C and associated fusion enthalpy of 234.59J/g indicative of anhydrous crystalline state of the drug.

Similarly for a dried film of Eudragit RS 30D, an exothermic peak was observed which begins at 369.62^{0}C and ends at 394.8^{0}C. Comparatively a small endothermic peak was observed at 454.02^{0}C.

For dried film of Eudragit RL 30D, a little broader exothermic peak was observed which begins at 361.75^{0}C and ends at 405.17^{0}C. Similarly, a small exothermic peak was noticed at 475.32^{0}C.

DSC thermogram was also recorded for the dried film of Ethylcellulose. Here, broad and comparatively smaller peak was observed. The peak begins 174.54^{0}C and ends at the 199.82^{0}C.

In the DSC thermogram of Aerosil® a broader exothermic peak was observed at 500.13^{0}C. For talc no peak was observed.

For formulations batches thermogram were recorded for the ratios up to 1:7 (D:P). For the formulation SF1 drug peak was observed beginning at 218.63^{0}C and ends at 236.66^{0}C. In the case of formulation SF2, the peak begins at 211.17^{0}C and ends at 239.08^{0}C. For the formulation SF3, SF4 and SF5 peaks begin at 214.22, 217.75 and 215.18^{0}C and the peaks ends at 234.15, 241.96 and 228.44^{0}C respectively. For the formulation SF5 (D:P-1:7) very small peak was obtained. This may be due to less concentration of the drug in this formulation.

In the preparations containing Eudragit RL 30D as coating material, for the formulation LF1 drug peak begins at 218.54^{0}C and ends at 239.45^{0}C. For other batches LF2, LF3, LF4 and LF5 peak begins at 209.18, 205.76, 211.31 and 212.04^{0}C and ends at 236.31, 234.01, 243.41 and 229.31^{0}C respectively.

Finally, in the microparticles containing Ethylcellulose (Surelease®) as a coating material, for pure Ethylcellulose an exothermic peak was observed, which begins at 174.54^{0}C and ends at 199.82^{0}C. For the formulation CF1, an exothermic peak of Ethylcellulose and a peak of Metformin Hydrochloride was observed. For the formulation CF3, CF4 and CF5 the intensity of both peaks was less.

In all the formulations either no shift or little shift in the peak had been observed which usually signify that there is no drug polymer or excipient interaction. This suggests that after getting encapsulated within the polymer coat, the drug remained in the crystalline state and dispersed in the form of molecular dispersion or solid solution (Barkai A, Pathak YV et al., 1990).

The physical state of the drug within the microparticles has an influence on the morphology and release kinetics from the microparticles (Soppimath, Kulkarni et al., 2001).

In all the formulations either no shift or little shift in the peak has been observed which usually signify that there is no drug polymer or excipient interaction. This suggests that after getting encapsulated within the polymer coat, drug remains in the original crystalline state and drug is dispersed in the form of molecular dispersion or solid solution [20].

The physical state of the drug within the microparticles has an influence on the morphology and release kinetics from the microparticles [21].

Powder X-Ray diffraction

A solid substance is characterized as either a crystalline or amorphous state. A crystal has a repetitious spacing of constituent atoms or molecules in a three dimensional array. Whereas the amorphous form has atoms or molecules randomly placed as in a liquid. Amorphous forms are of higher thermodynamic energy than the crystalline form, solubilities as well as dissolution rates are higher. Due to the random arrangement of atoms and molecules the energy required for separation is low; hence more solubility is exhibited by amorphous solids. Absorption and ultimately bioavailability is affected by extent of absorption.

The characteristic peaks of the drug can be observed around 2θ values of 17, 22, 24, 28 and 34. The formulations containing Eudragit RS 30D (SF Series), for the formulation FS 1, drug peaks at 2θ values of 17, 22, 34 were observed but with the less intensity. This may be due to the less concentration of the drug in the formulation in comparison to the pure drug. For the formulation SF 2 and SF 5 drug drug peaks were observed with varying intensity. This suggests that in the formulations drug remains in the crystalline state, it doesn't transform into amorphous state.

For the formulations containing Eudragit RL 30D as rate controlling polymer (LF series), various drug peaks are observed, again suggesting that the drug remains in a crystalline state.

For the formulations containing Ethylcellulose (CF series), drug peaks with variation in the intensity can be observed.

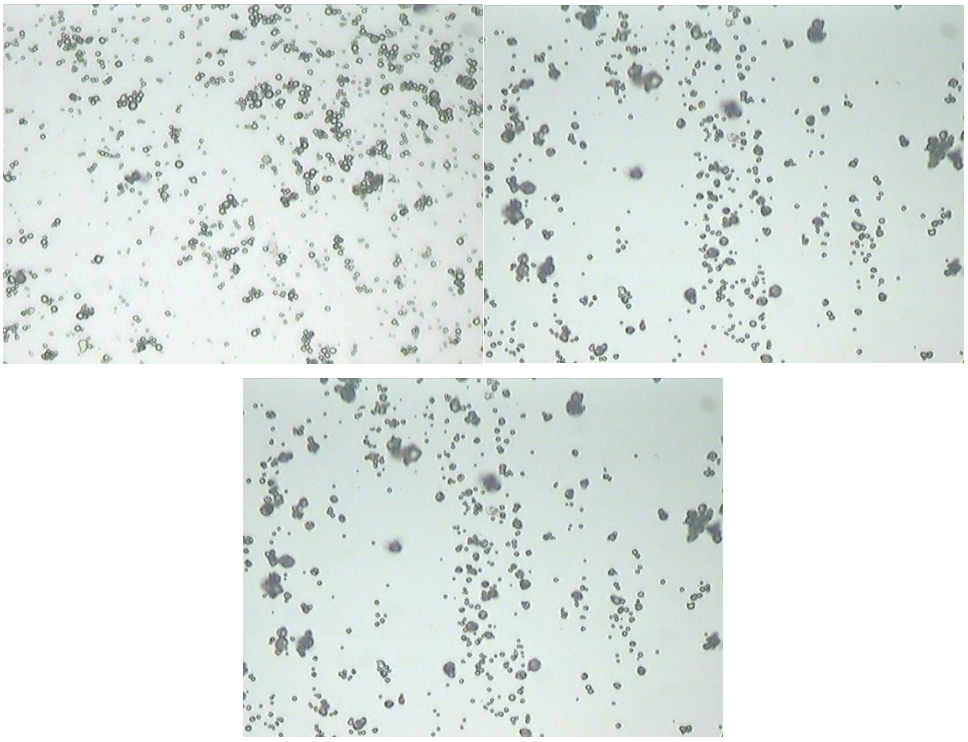

Fig. 1: Images of microparticles from camera fitted with optical microscope (Motic®).

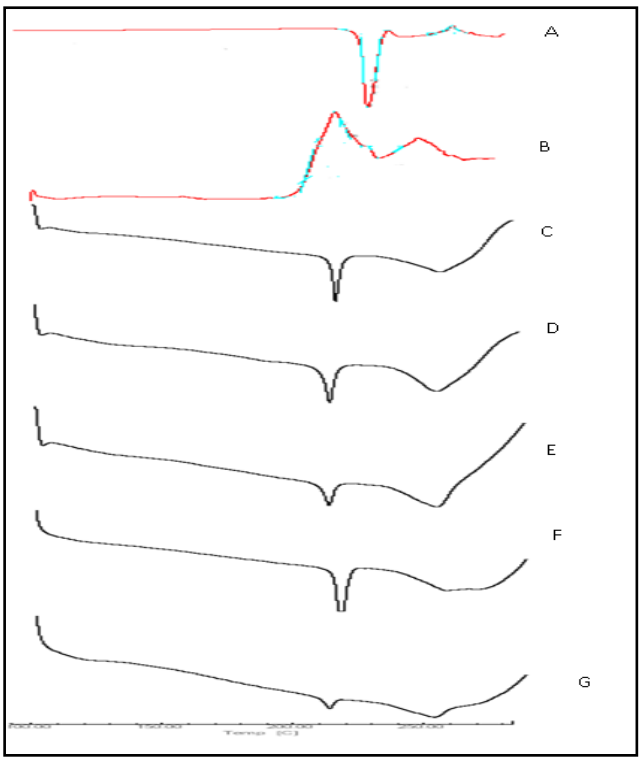

Fig. 2: DSC thermograms of LF Series of formulations, A) Pure drug, B) Pure polymer, C) LF1, D) LF2, E) LF3, F) LF4, and G) LF5.

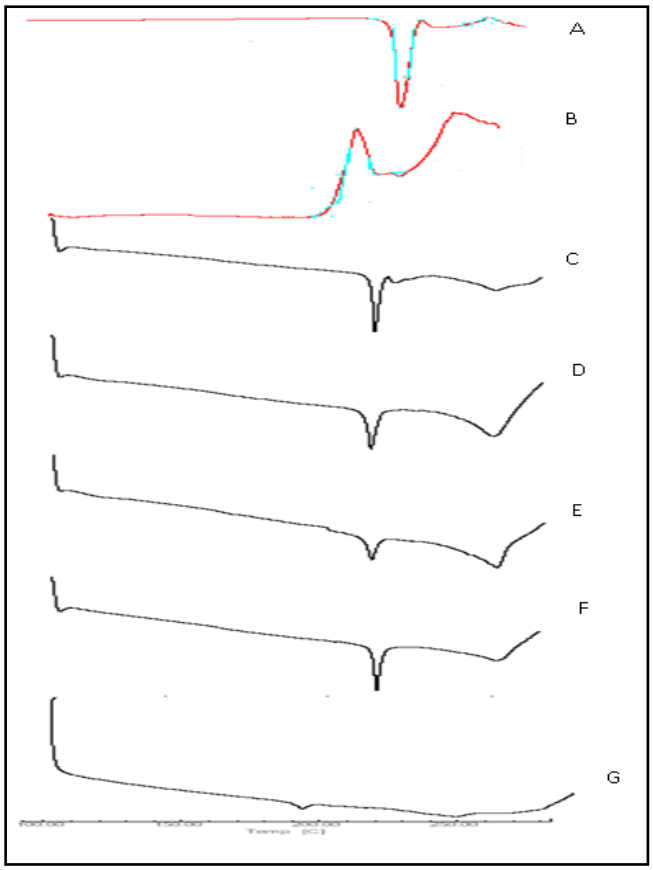

Fig. 3: DSC thermograms of SF Series of formulations, A) Pure drug, B) Pure polymer, C) SF1, D) SF2, E) SF3, F) SF4, and G) SF5.

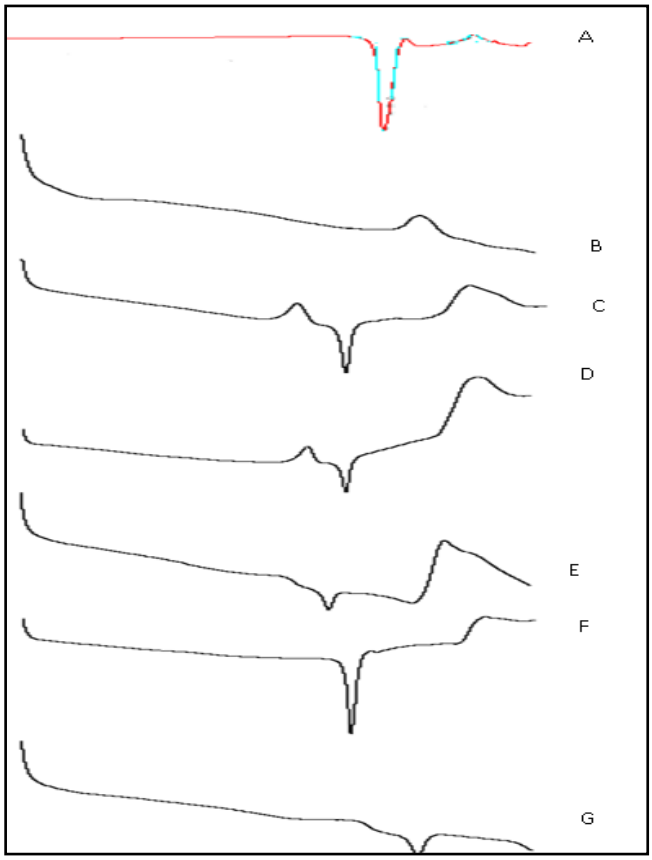

Fig. 4: DSC thermograms of CF Series of formulations, A) Pure drug, B) Pure polymer, C) CF1, D) CF2, E) CF3, F) CF4, and G) CF5.

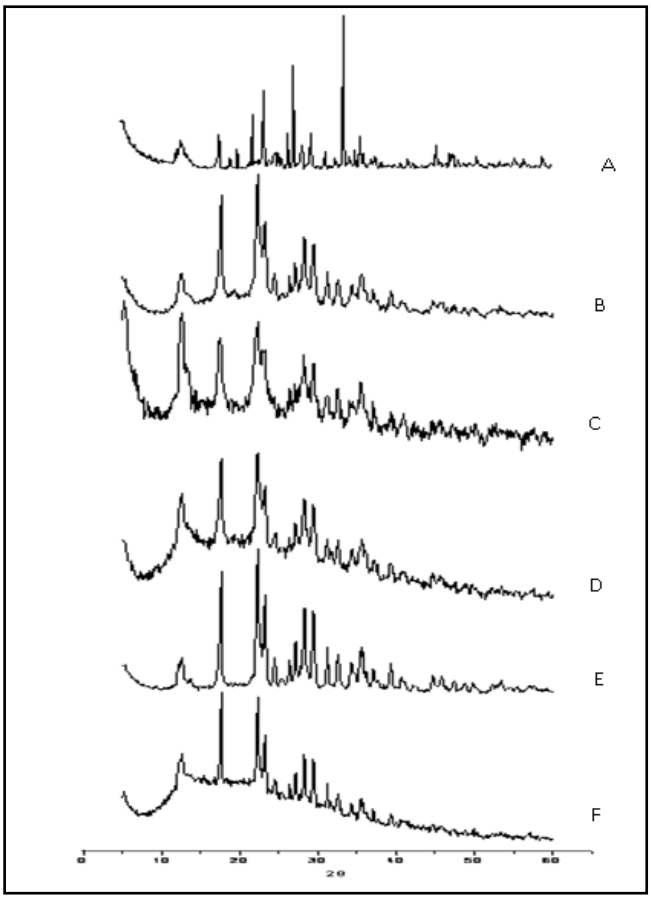

Fig. 5: Images of X-ray diffraction pattern A) Pure Drug, B) LF1, C) LF2, D) LF3, E) LF4, F) LF5

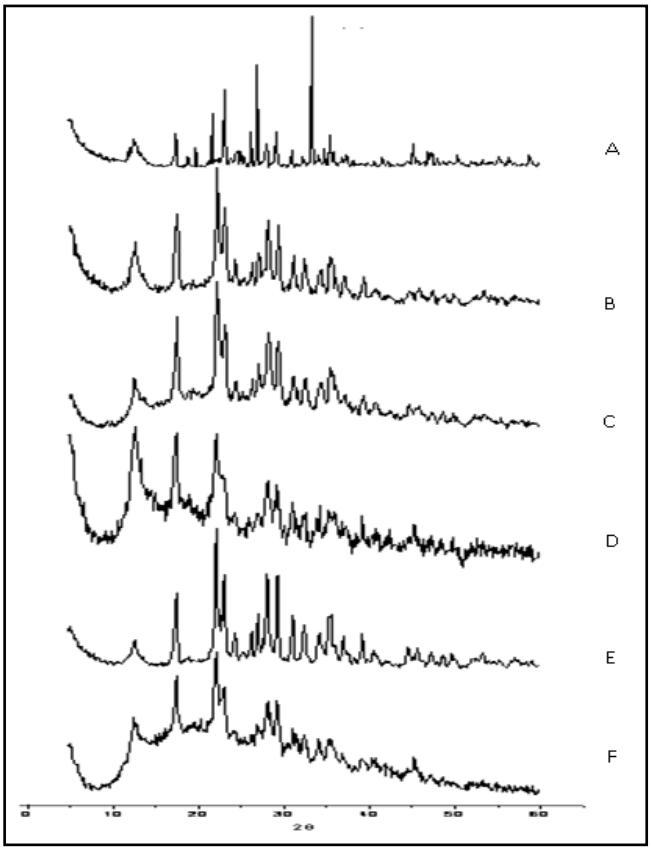

Fig. 6: Images of X-ray diffraction pattern A) Pure Drug, B) SF1, C) SF2, D) SF3, E) SF4, F) SF5

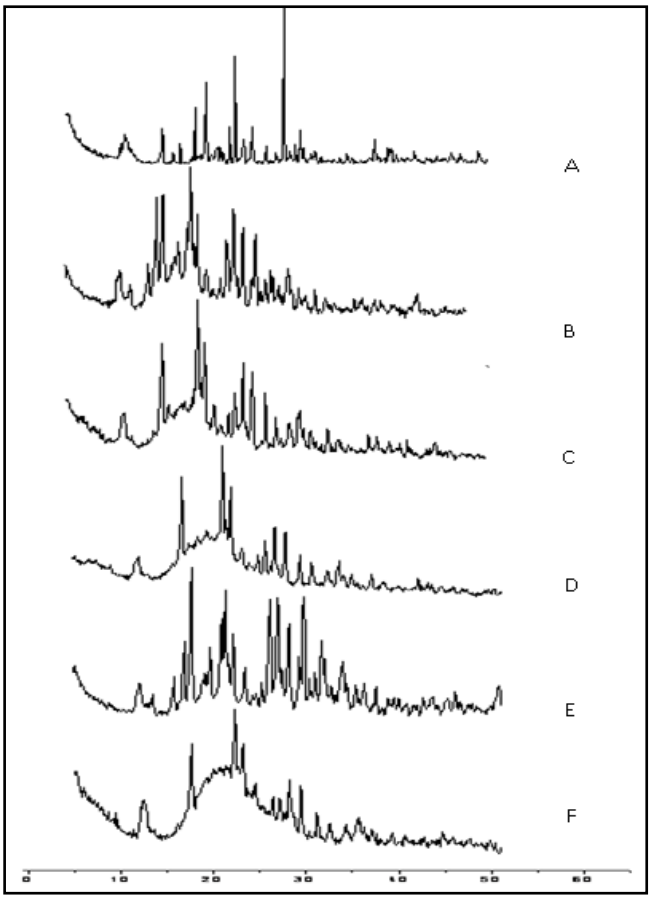

Fig. 7: Images of X-ray diffraction pattern A) Pure Drug, B) CF1, C) CF2, D) CF3, E) CF4, F) CF5

Scanning electron microscopy

Scanning electron microscopy was utilized to observe surface properties and as well as particle size of microparticles. SEM images were taken at the magnification of 3000X. As it can be seen from the images that, in the case of Ethylcellulose coated microparticles, small as well as intermediate sized particles can be observed. The particles are in the form of agglomerates, the results are consistent with earlier published work by some research group [16], and particles are of irregular shape, while few spherical particles can also be observed. In the case of Eudragit RL30D coated microparticles, shriveling and folding was observed at the surface. This surface morphology may be formed uneven shrinkage forces during the drying of droplets, depending on the viscosity of the liquid feed. The tendency to shrive or fold increases with the increase of feed viscosity [18]. Most of the particles were below 5 µm and they were not spherical in shape. The larger particles can also be observed in the image. SEM images for Eudragit RS30D coated microparticles clearly show that many particles are spherical or close to spherical shape with particle size below 5 µm, larger particles are also seen. In comparison to Eudragit RL30D microparticles shriveling and folding was less. Very few particles were observed with shriveling and folding.

***In-vitro* dissolution testing**

When D:P (Drug : Polymer) ratio used was 1:1, for all the formulations of the same ratio almost complete drug release took place by the end of the 360 min. (6 Hrs). Except for formulation CF1 where the complete drug has happened at the end of the 240 min. (4 Hrs). At this ratio slower release of was observed for Eudragit RS30D coated microparticles, followed by Eudragit RL30D coated microparticles. When D:P is decreased to 1:2 better control of the drug release was observed for all the formulations. In the entire formulations complete drug release was observed to take place at the end of the 480 min. (8 hrs). At this ratio marginally slower drug release was observed again for microparticles formed by coating of Eudragit RS30D. But again the difference in the drug release was very low. At the D:P ratio 1:3 not much difference was observed in controlling the release of the drug for all the formulations under this ratio. Further the D:P ratio decreased to 1:5 to evaluate its effect on the release of the freely water soluble drug. Here better control over the drug release was observed, if compared to previously prepared ratios. In the case of Eudragit Rs30D coated microparticles Drug release lasts up to 720 min. (12 Hrs). Similarly formulations prepared with Eudragit RL 30D and Surelease the complete drug release took place at the end of 12 hrs. Very small amount of the drug was released after 12 hrs, here, dissolution testing was carried out for 24 hrs. At D:P ratio 1:7 control over drug release was increased. Here, the Controlled drug release was obtained for 24 hrs. Better control over drug release was observed for Eudragit RS30 D coated microparticles. At the end of the 12th hr the % drug release was 94.82%, for formulation LF5 drug release was 97.11% and for formulation CF5 drug release was 98.56%. As there was a decrease in D:P ratio, or if the polymer concentration is increased better control over release of water soluble drugs can be achieved. The D:P ratio was further taken as 1:9, dissolution profiles clearly indicates that drug release has delayed. For formulation SF6 drug release was 83.29% at the end of 12th hour. For the formulation LF6 and CF6 the drug release was 92.96 and 96.97 respectively. Here, the slower drug release was obtained by the formulation where polymer used was Eudragit RS30D. Eudragit RS types of polymers are hydrophobic in nature and their water permeability is less in comparison to Eudragit RL types of polymers, because of the amount of quaternary ammonium groups of Eudragit RS is lower than that of Eudragit RL [22]. Hence it can be concluded that this polymer impart better control on drug release though the drug is hydrophilic in nature. When microspheres were prepared by using Eudragit RSPO by solvent evaporation method (data not shown here), the drug release is extended up to 48 hrs. This extended drug release with the same polymer is achieved because of the thickness of the coating present,

which is not as thick in case of microparticles prepared by spray-drying technique. Finally, the D:P ratio was extended to 1:11, to see whether drug release can be controlled further or not. It was observed that at the end of 12th hr 78.74% of the drug was released for Eudragit RS30D microparticles. For formulation LF7 and for CF7 drug release was 94.34 % and 92.26 % respectively. Hence, as there was decrease in D:P ratio release of the drug was delayed further in all the preparations, but SF series of formulations where Eudragit RS30D was used as a coating polymer showed the better results.

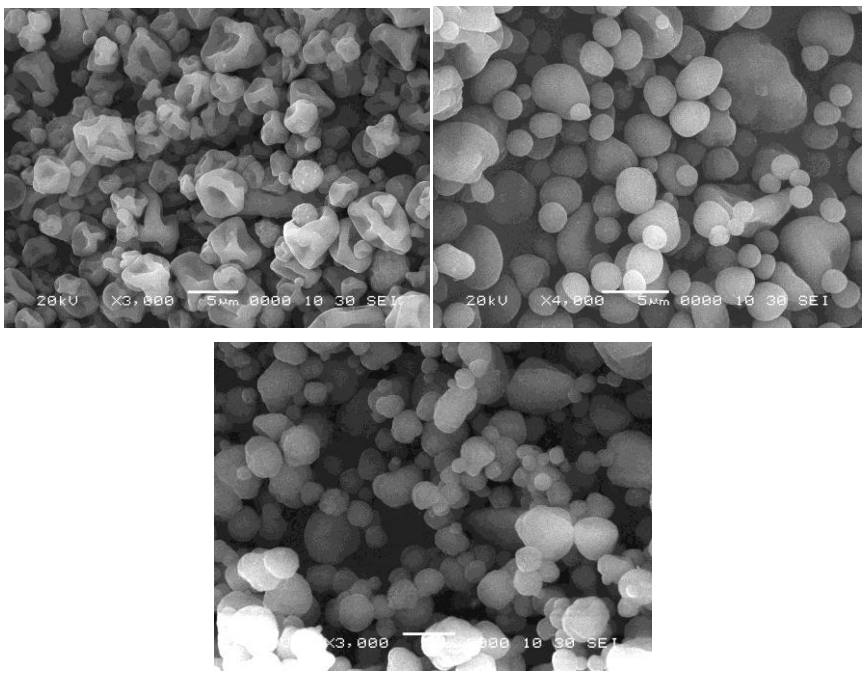

Fig. 8: SEM images of formulations LF1, SF1 and CF 1 respectively.

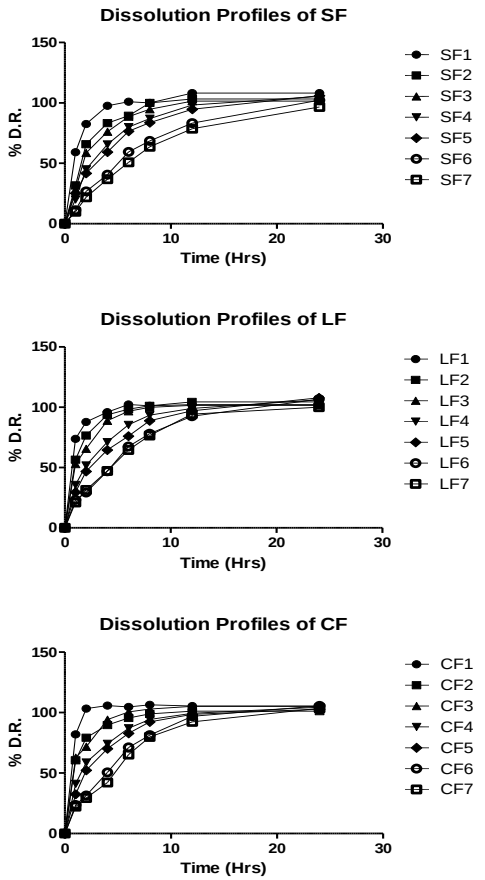

Fig. 10: Comparative Dissolution Profiles

Fig. 10: Comparaive Dissolution Profiles

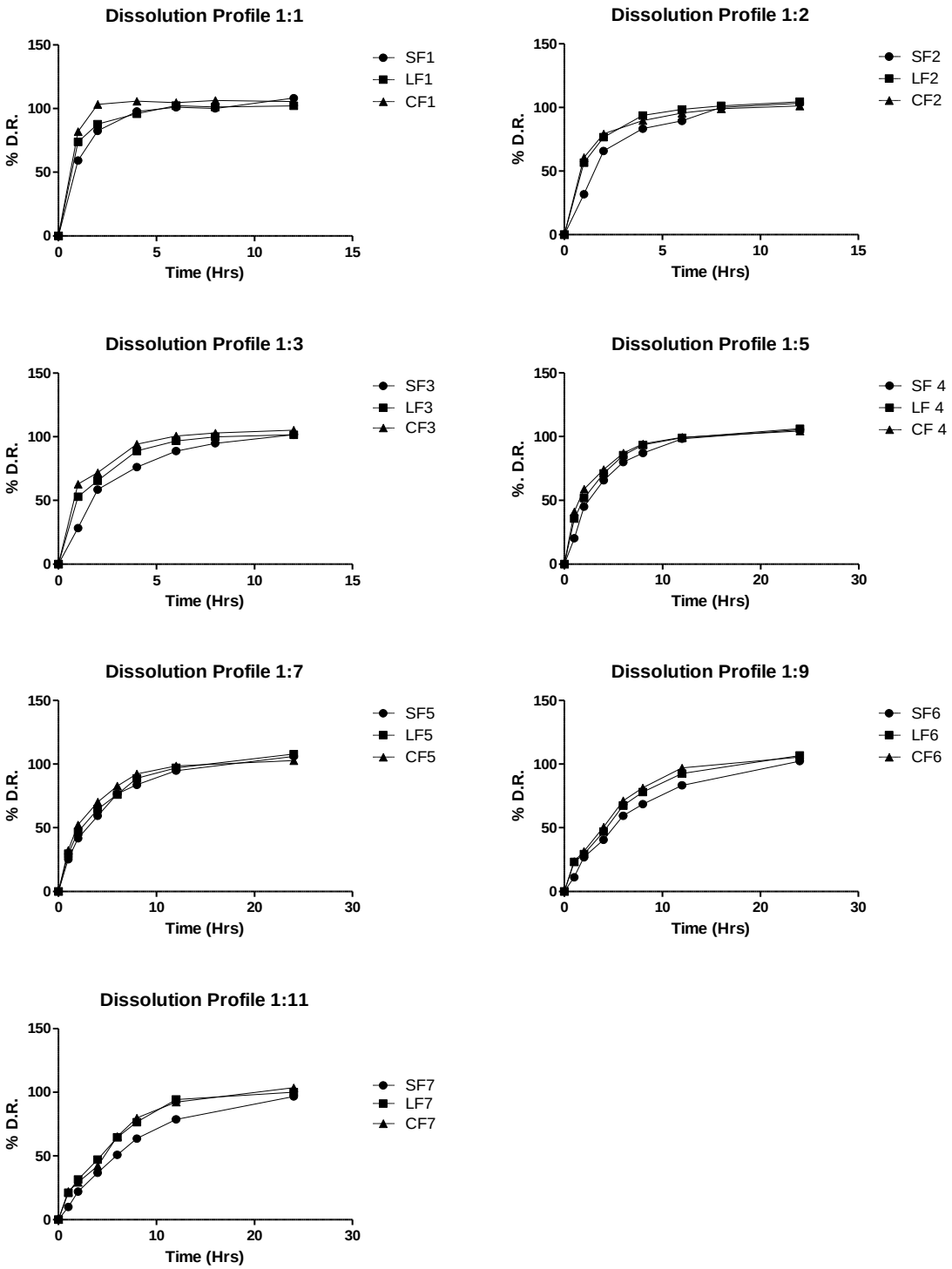

Fig. 9: Dissolution Profiles of all D:P Ratios

CONCLUSION

It may be concluded that with the help of spray-drying technique controlled release microparticles can be obtained for hydrophilic drug. Encapsulation efficiency was not affected by D:P ratio. Eudragit RS 30 D showed better control of release of drug compared to other aqueous polymeric dispersions.

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