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Research Article

STUDY ON EFFECT OF SOLVENTS AND NON-SOLVENTS ON THE RELEASE OF DRUG FROM MICROCAPSULES PREPARED BY VARIOUS COACERVATION PHASE SEPARATION TECHNIQUES

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ABSTRACT

The study was to determine the effect of solvents like acetone, dimethyldigol, 1,4-dioxan and non-solvents like n-hexane and chloroform on microencapsulation of paracetamol. Microcapsules were prepared by following coacervation phase separation like solvent evaporation and non-solvent addition method with rate retarding cellulose polymers using various non- aqueous and non solvents. Microcapsules were characterized for the particle size and shape by scanning electron microscopy, angle of repose, bulk density, percent drug content, entrapment efficiency and *in vitro* dissolution studies. Drug excepient compatibility was determined by Infrared Spectroscopy and Differential Scanning Calorimetry. Accelerated stability studies were also carried out following ICH Guidelines. Scanning electron microscopy revealed that microcapsules were found spherical, free flowing and porous. The entrapment efficiency and wall thickness was found in between 61.18% & 97.31%, 126.198µ & 65.161µ respectively. The drug release was extended maximum upto 12hours with cellulose acetate using 1,4-dioxan, and upto 12 hours with cellulose acetate phthalate using 1,4-dioxan and dimethyldigol which effected over size and release kinetics. Infrared spectroscopy and Differential scanning Calorimetry results showed paracetamol was compatible with excepients. The curve fitting data revealed that the release followed first order kinetics and higuchi's and peppas plots stated non-fickian and diffusion controlled.

Keywords: Microcapsules, Paracetamol, Cellulose polymers, Solvents, Non solvents, Coacervation-phase-seperation.

INTRODUCTION

Microencapsulation is defined as the application of a thin coating to individual core material that have an arbitrary particle size range from 5 to 5000µm.[1, 2] This coating can retard the release of a drug,[3] modify the availability of the core and promote sustain release, change the cores chemical properties such as solubility and reactivity and physical properties such as color, and particle size,[4] alter the heat sensitivity and photosensitivity of the core.[5] Microencapsulation can improve the absorption of a drug and reduce side effects such as irritation of the gastric intestinal mucosa.[6]

Cellulose acetate phthalate (CAP) and cellulose acetate (CA) is widely used as a coating material for tablets and capsules. Several researchers have investigated the use of CAP and CA as polymer.[7-9] Non-aqueous [10-12] manufacturing vehicles in microencapsulation of a drug by a coacervation phase separation procedure were reported.

The solvent evaporation method and non-solvent addition method has been reported by many others.[13-15] However no study was made on the use of solvents like dimethyldigol and 1, 4-dioxan as a solvent to prepare polymer solution.

MATERIALS AND METHODS

Materials

Paracetamol was obtained as a gift sample from Nitin pharma (karnal). Cellulose acetate phthalate and Cellulose acetate was obtained from Natco pharma (AP). All the solvents are procured of Merck.

Methods

Preparation of microcapsules

The microcapsules are prepared by three different methods with three different solvents and two non-solvents. In each of these techniques paracetamol microcapsules were prepared with CAP and CA as coating agents. Acetone, dimethyldigol, 1, 4-dioxan was used as solvent and chloroform and n-Hexane was used as non-solvent and Liquid paraffin as the encapsulating vehicle. Three batches of paracetamol microcapsules were prepared with each polymer and with each technique Table No.1.

Method-I: In this method the polymers was dissolved in acetone, by stirring the mixture at 800rpm the author dispersed paracetamol particles in liquid paraffin that contained 1% w/w polysorbate. The polymer solution was added slowly to the drug dispersion by means of a burette. The mixture was agitated at room temp (25°C) until the acetone (polymer solvent) was evaporated. The rate of stirring was kept constant for all the batches and for all the methods and the ratio of drug to polymer was varied as (D:P as 1:1, 1:2, 1:3) labeled as CAPM 1, 2, 3 and CAPPMA 1, 2, 3. The liquid paraffin was decanted and the microcapsules were collected, washed with petroleum ether to remove any remaining oil phase and dried under, reduced pressure for at least 12 hours.

METHOD-II: This procedure is similar to the method-I except that the solvent was replaced by dimethyldigol instead of acetone. After the addition of polymer solution a non-solvent (chloroform) of 50ml was added from a burette for a period 30 minutes. Agitation of liquid paraffin containing paracetamol, polymer solution and chloroform then was performed for 20min. Microcapsules collection procedure was the same as described for method-I. The microcapsules are labeled as (CAPMM 1, 2, 3 and CAPPMM 1, 2, 3).

METHOD-III: The procedure was similar to method-I except that 1,4-dioxan was used as a solvent for dissolving the polymer and a non-solvent n-Hexane was added to the liquid paraffin (50ml) that contained dispersed paracetamol particles for a period of 30 min. The microcapsules collection procedure was the same as described method-I. The formulations were coded as CAPMD 1, 2, 3 for cellulose polymer and CAPPMD 1, 2, 3 for cellulose acetate phthalate polymer.

Table 1: Formulation composition

Ingredient	Method-I			Method-II			Method-III		
Formulation	CAPMA1	CAPMA2	CAPMA3	CAPMM1	CAPMM2	CAPMM3	CAPMD1	CAPMD2	CAPMD3
Paracetamol	1 gm	1 gm	1 gm	1 gm	1 gm	1 gm	1 gm	1 gm	1 gm
CA	1 gm	2 gm	3 gm	1 gm	2 gm	3 gm	1 gm	2 gm	3 gm
Acetone	30ml	30ml	30ml	--	--	--	--	--	--
Dimethyldigol	--	--	--	30ml	30ml	30ml	--	--	--
Chloroform	--	--	--	50ml	50ml	50ml	--	--	--
1,4-dioxn	--	--	--	--	--	--	30ml	30ml	30ml
n-hexane	--	--	--	--	--	--	50ml	50ml	50ml
Formulation	CAPPMA1	CAPPMA2	CAPPMA3	CAPPMM1	CAPPMM2	CAPPMM3	CAPPMD1	CAPPMD2	CAPPMD3
Paracetamol	1 gm	1 gm	1 gm	1 gm	1 gm	1 gm	1 gm	1 gm	1 gm
CAP	1 gm	2 gm	3 gm	1 gm	2 gm	3 gm	1 gm	2 gm	3 gm
Acetone	30ml	30ml	30ml	--	--	--	--	--	--
Dimethyldigol	--	--	--	30ml	30ml	30ml	--	--	--
Chloroform	--	--	--	50ml	50ml	50ml	--	--	--
1,4-dioxn	--	--	--	--	--	--	30ml	30ml	30ml
n-hexane	--	--	--	--	--	--	50ml	50ml	50ml

Characterization of microcapsules

Scanning electron microscopy (SEM)

Morphological characterization of the microcapsules was carried using scanning electron microscopy (SEM-S3700N). For SEM the double – sided sticking tape coated with gold film (thickness 200nm) was used under the reduced pressure (0.001torr).

Particle size analysis

All the batches prepared were analyzed for particle size; microcapsules were placed on the set of standard sieves ranging from sieve No. 16# – 60#. The sieves were arranged in such a way that in descending order of the mesh size 16# on the top and 60# mesh in the bottom. The microsphere passed through the set of sieves and the amount retained on each sieve was weighed and the average mean diameter was determined. The data is given in Fig. 1.

Angle of repose

A funnel was fixed in a stand in such a way the top of the funnel was at a height of 6cms from the surface. The microcapsules were passed from the funnel so that they form a pile. The height and the radius of the heap were measured and the angle of repose was calculated using the equation.

$$\emptyset = \quad h/r$$

Assay of Paracetamol

To determine the total drug content of the microcapsules 100mg of microcapsules was ground to a fine powder and dissolved in 5ml of acetone and diluted with phosphate buffer PH 7.4 to 100ml. the drug content was determined spectrophotometrically at 245nm. Three determination of the microcapsules content from the same batch for each ratio and method was performed. The data is represented in Fig. 2.

Encapsulation efficiency (EE)

Drug loaded microcapsules were weighed and dissolved in phosphate buffer PH 7.4 and mixture was filtered. The percent entrapment was calculated using the Eq (1). The rate is represented in Fig. 2.

$$\text{Encapsulation efficiency} = \frac{\text{Actual drug content} \times 100}{\text{Theoretical drug content}} \quad \text{Eq (1)}$$

Wall thickness

The wall thickness of the prepared microcapsules was calculated using the Eq (2):

$$h = ř\,(1\text{-}P)\,d_1/3(Pd_2 + (1\text{-}P)\,d_1 \quad \text{Eq (2)}$$

Fourier transforms infrared spectroscopy (FT-IR)

The FT-IR spectra acquired were taken from dried samples. An FT-IR (8600 S) spectrometer was used for the analysis in the frequency range between 4000 and 400 cms^{-1}.

Differential scanning calorimetry (DSC)

DSC was performed on paracetamol, drug loaded microcapsules using Seiko (Japan) DSC model 220c. Samples were sealed in aluminium pans and the DSC thermo grams were reported at a heating rate of 10°/min from 20°C to 200°C.

In vitro drug release studies

In vitro dissolution studies were performed using (USP type II dissolution apparatus). The rotating basket method specified in USP-XXI at 75 rpm. The microcapsules were weighed and tied in the muslin bag and placed in the basket. The dissolution medium (900ml) consisted of 0.1M hydrochloric acid for the first 2 hours and then changed to phosphate buffer pH 7.4 from the 3rd hour. The temperature was maintained at 37°C. An aliquot of (5ml) sample was withdrawn at specified time interval and replaced with an equivalent volume of dissolution fluid. Drug content was determined by UV-Visible spectrophotometer (Schimazdu UV 1700 E 23) at 245nm. The release studies were conducted in triplicate and the results are showed in Fig. 3.

Determination of stability of the microcapsules

The microcapsules prepared in the present study were filled in the hard gelatin capsules (No-1) and stored in HDPE container at RT 37°C, and 45°C for 6 months as per ICH guidelines. The samples were then characterized for % drug content. The results are summarized in the Table No. 4.

RESULTS

Prepared microcapsules were found to be discrete, spherical and free flowing and have nearly uniform size. SEM Fig. 4. Among the various formulations the formulation CAPPMD1 and CAPPMA3 showed maximum percentage yield and CAPMD1 formulation showed highest drug entrapment Fig. 2. The average mean diameter of the microcapsules was found to be ranging between 65.16 to 126.198 µm showed in Table No.2. The IR spectra of the pure drug and microcapsules with polymers were compared and the characteristic peak for microcapsules in spectra was found to be super imposable to that of the pure drug. There were no extra peaks, which gives evidence that there was no drug polymer interaction. Maximum release of paracetamol from the various formulations was achieved with in 12-14 hours or longer Fig. 3. The release mechanism of the paracetamol formulation was determined by comparing their respective correlation coefficients. Drug release from microcapsules prepared by II and III methods gave good sustained release when compared to method I. from the release profiles it can be understood that the solvent used for polymer solution influences the rate of release of the drug. The microcapsules

prepared with 1, 4-dioxan and dimethyldigol sustained the drug release for more than 12hours when compared to acetone. The formulation of CAPMD3, CAPPMD3 and CAPPMM3 showed good release.

Table 2: Various characteristics of microcapsules

Formulation	%DC ± SD	Angle of repose	BD g/cc	AMD µ	Wall thickness µ
CAPMA1	82.35±1.782	24.15	0.609	333.63	65.16
CAPMA2	77.27±1.562	25.33	0.614	346.80	66.73
CAPMA3	79.65±1.098	27.75	0.622	350.79	67.5
CAPPMA1	81.78±1.071	25.01	0.491	433.99	85.98
CAPPMA2	78.70±1.305	25.87	0.580	437.98	86.77
CAPPMA3	78.54±0.708	24.13	0.45	450.27	89.21
CAPMM1	77.69±1.261	29.05	0.468	407.0	78.31
CAPMM2	75.54±0.788	23.96	0.46	416.47	80.12
CAPMM3	72.21±0.817	22.02	0.487	431.01	82.93
CAPPMM1	65.78±0.839	26.15	0.486	501.11	99.28
CAPPMM2	61.18±1.209	25.19	0.509	506.41	100.33
CAPPMM3	63.39±0.555	27.33	0.491	519.15	102.86
CAPMD1	97.31±1.559	24.76	0.466	552.85	106.38
CAPMD2	93.90±0.765	24.43	0.496	571.16	109.9
CAPMD3	95.82±0.601	23.26	0.506	574.99	110.64
CAPPMD1	93.44±1.043	20.62	0.428	584.29	115.76
CAPPMD2	92.16±0.499	18.43	0.412	585.66	116.02
CAPPMD3	89.25±1.231	17.46	0.315	636.93	126.19

DISCUSSION

The formulation followed first order release kinetics, higuchi and peppas release plots stated non-fickian and diffusion controlled Table No. 3. The release mainly depended on the ratio of the polymer and also the method of preparation technique used. In paracetamol spectrum C-H stretching band at 945cm^{-1}, O-H stretching was found as broad band was found at 3200cm^{-1} and O-H bending at 945cm^{-1}, N-H bending bands were found at 1600cm^{-1}. The same bands were also found in the spectra of the formulations indicating that there was no drug-polymer interaction Fig. 6. The DSC Thermo grams proved the compatibility of the drug and polymers used where no deviations were found in the graph of the drug with polymer in comparison with pure drug and the mid point of the peak was found at same temperature in between 155ºC - 165ºC Fig. 5. The accelerated stability studies showed the stable nature of the drug and showed a good correlation between the original and the aged samples Table No. 4. Good entrapment efficiency was observed. SEM demonstrated the spherical nature of the microcapsules and the presence of the drug particles on the surface Fig. 4.

Table 3: Kinetic values of drug release for all formulations

Formulation	First-order equation		Higuchi's equation		Peppas equation	
	Slope	Regression coefficient (R^2)	Slope	Regression coefficient (R^2)	Slope	Regression coefficient (R^2)
CAPMA1	-0.003	0.826	3.813	0.900	0.281	0.850
CAPMA2	-0.002	0.796	3.272	0.846	0.274	0.821
CAPMA3	-0.002	0.940	3.775	0.944	0.329	0.919
CAPPMA1	-0.005	0.9910	4.035	0.946	0.553	0.942
CAPPMA2	-0.003	0.983	4.303	0.948	0.448	0.932
CAPPMA3	-0.003	0.908	3.692	0.979	0..437	0.961
CAPMM1	-0.002	0.756	3.196	0.9883	0.246	0.966
CAPMM2	-0.002	0.911	3.408	0.939	0.289	0.972
CAPMM3	-0.001	0.923	3.306	0.956	0.298	0.986
CAPPMM1	-0.031	0.804	3.787	0.968	0.291	0.961
CAPPMM2	-0.001	0.982	2.894	0.986	0.262	0.962
CAPPMM3	-0.001	0.968	2.803	0.989	0.285	0.976
CAPMD1	-0.001	0.862	3.528	0.934	0.386	0.942
CAPMD2	-0.002	0.931	4.024	0.982	0.480	0.984
CAPMD3	-0.001	0.970	3.706	0.994	0.493	0.992
CAPPMD1	-0.004	0.880	3.168	0.852	0.280	0.880
CAPPMD2	-0.001	0.883	3.935	0.941	0.387	0.936
CAPPMD3	-0.001	0.968	3.740	0.962	0.404	0.962

Table 4: Accelerated stability data for microcapsules at various temperatures after storing for 6 months

Formulation	% Drug content before storage	% Drug content RT	% Drug content 37°C	% Drug content 47°C
CAPMD3	96.16	96	95.5	95.2
CAPPMM3	63.2	63.02	62.8	61.1
CAPPMD3	89.04	89.01	88.6	86.22

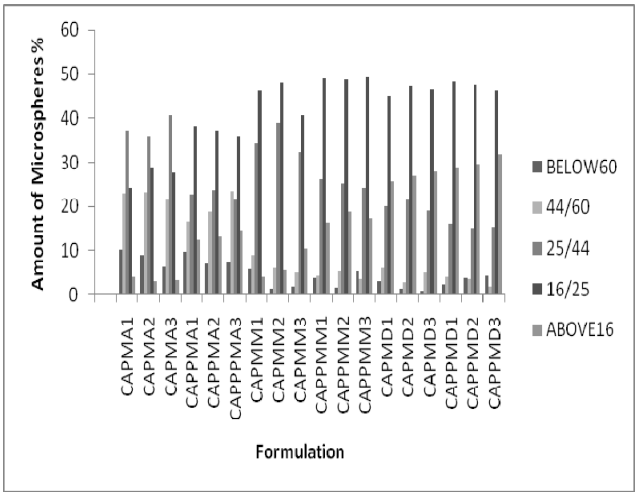


Fig. 1: Sieve analysis graph

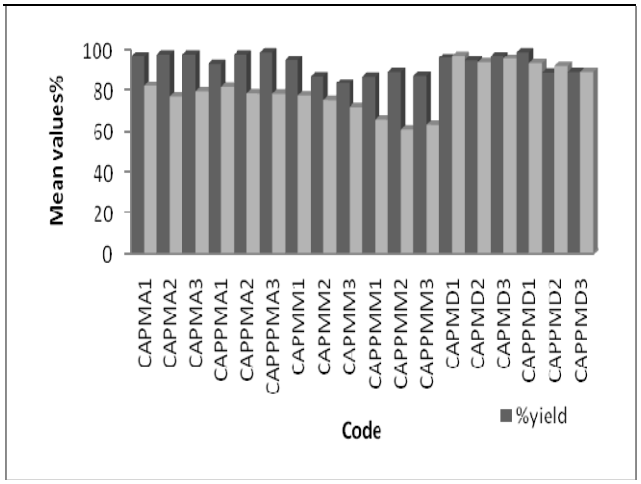


Fig. 2: Graph representing % yield and % entrapment efficiency.

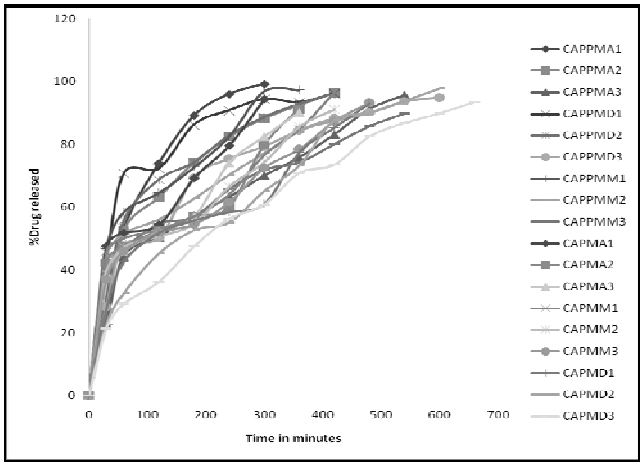
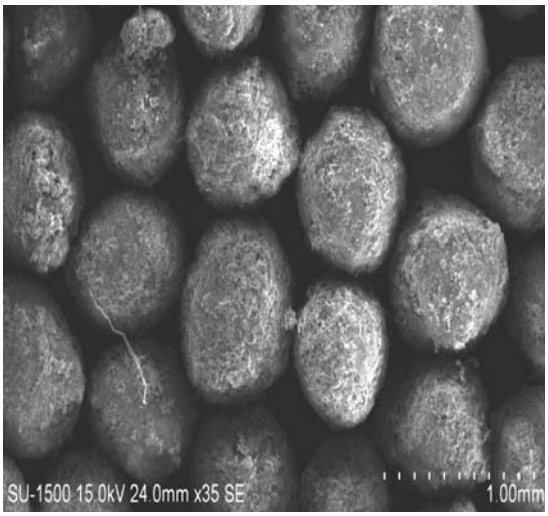
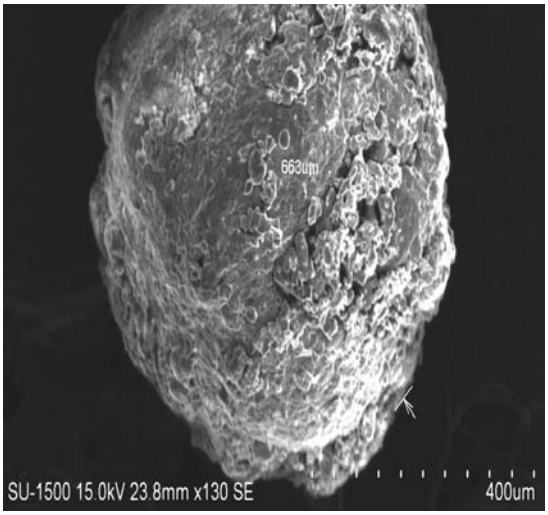


Fig. 3: Cumulative % release vs time plots of paracetamol microcapsules.





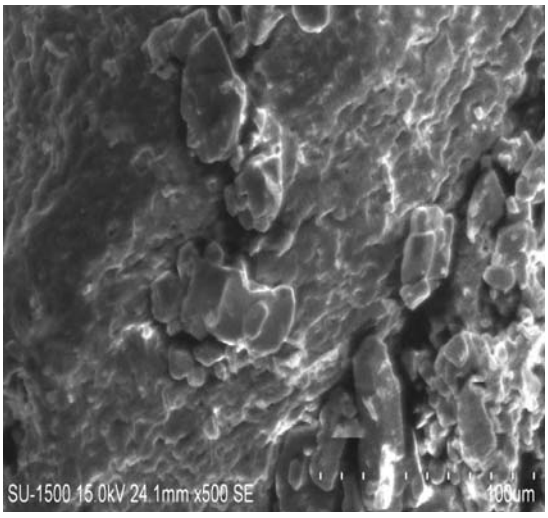


Fig. 4: SEM photographs of CAPPMD3

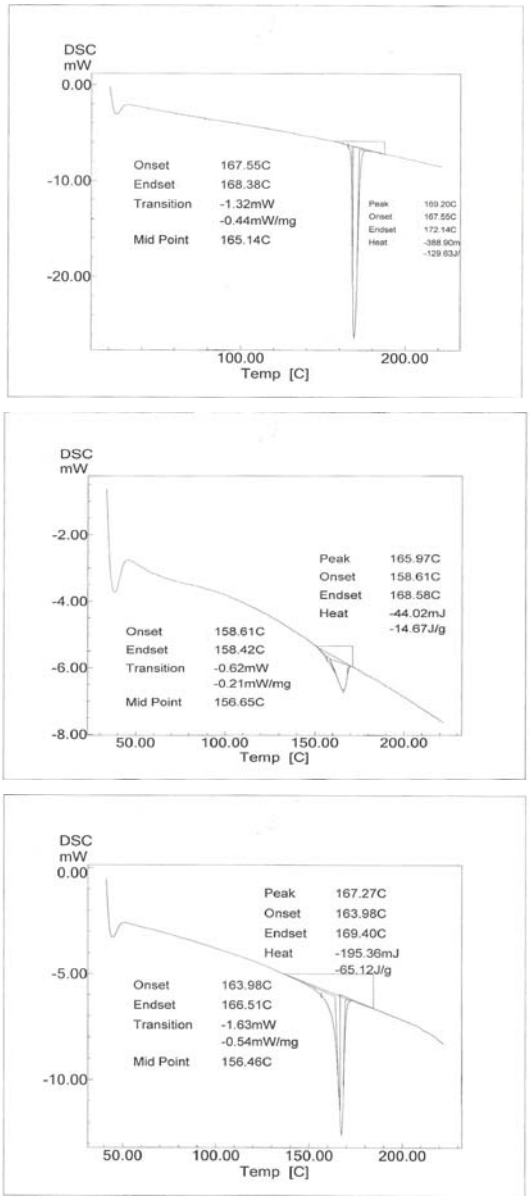


Fig. 5: DSC thermo grams of paracetamol microcapsules with different polymers, Pure Drug, Drug+CAP, Drug+CA.

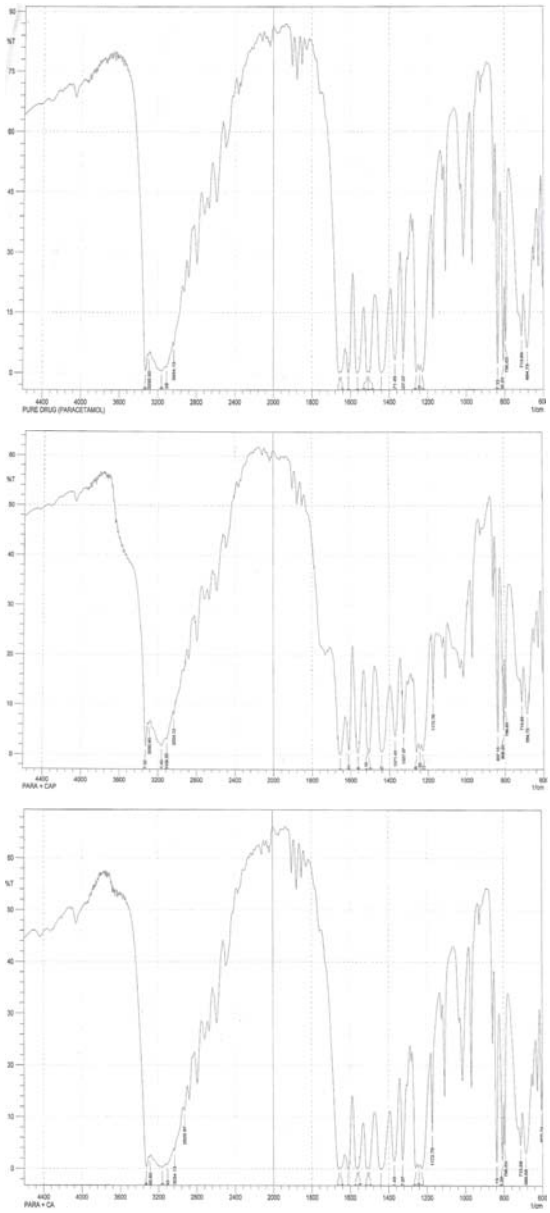


Fig. 6: FT-IR patterns of Pure Drug, Drug +CAP, Drug +CA

CONCLUSION

The paracetamol microcapsules sustained drug release for 12 hours or longer. This retard release of the drug can be related to the size of the microcapsules. The size of the microcapsules prepared with dimethyldigol and 1, 4- dioxan have high mean diameter when compared to the acetone. It can be concluded that the technique used and the type of solvent and non-solvent has an effect on the entrapment of drug as well as on the drug release. No drug polymer interaction was found and formulations remained stable over a long period of time.

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