Research Article

ANTIEPILEPTIC SUSTAINED RELEASE CARBAMAZEPINE MICROCAPSULES FOR KIDS

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Accepted on: 01-02-2011; **Finalized on:** 10-04-2011.

ABSTRACT

The aim of present work was to formulate and evaluate microencapsulated sustained release preparation of carbamazepine, for kids using various polymers such as ethyl cellulose, Eudragit RS and Eudragit RL as the retardant material to extend the release. Microcapsules were formulated by Emulsification – Solvent – Evaporation technique in varying drug to Polymer ratio. The microcapsules were uniform, free flowing and spherical showed by SEM, having a size range of 127 – 321 µm. Method showed good encapsulation efficiency in the range of 83 – 94%. In vitro release studies revealed the effect of drug to polymer ratio. Drug release rates were considerably lower then unencapsulated carbamazepine which was the main aim. FT-IR spectroscopy confirmed that there is no interaction between drug and polymer. It was observed that the microcapsules were stable at 40^0C. Of the three polymers studied, microcapsules formulated with ethyl cellulose showed good release and encapsulation efficiency followed by Eudragit RL.

Keywords: Microcapsules, carbamazepine, ethyl cellulose, Eudragit RS and Eudragit RL.

INTRODUCTION

Microencapsulation is used to modify and retard drug release. The microcapsules offer advantage that the coated particles can be widely distributed throughout the gastrointestinal tract. Application of microcapsules include odor and taste masking[1], for converting liquid drugs in free flowing powder[2], for sustained or prolong drug release[3], to formulate incompatible drug and to reduce toxicity and GI irritation, to alter site of absorption[4].

Carbamazepine is used as an antiepileptic drug for kids, having narrow therapeutic window (4 – 12 µg/mg). The drug is more than 70% bound to plasma protein and has long half-life. But it induces its own metabolism, hence $t_{½}$ on repeated dosing decreases and is shorter in children[5].

An extensive literature survey showed that, solvent – evaporation method has been applied to polymers like ethyl cellulose[6], Eudragit RS and Eudragit RL.[7] The permeability of drug release through their coating films is independent of pH of GIT.

MATERIALS AND METHODS

Materials

Carbamazepine was supplied by Amoli Organics Ltd; Eudragit RS and RL and Ethylcellulose were gift samples from Zim Laboratories Pvt. Ltd. Nagpur. Other reagents were all of analytical grade.

Preparation of Microcapsules

Weighed quantity of polymer was dissolved in 30 ml of acetone. Drug was then dispersed in polymer phase resulting mixture was then emulsified by adding drop wise in liquid paraffin containing 1.3% w/v SPAN 80 with continuous stirring at 1500 rpm using Remi medium duty stirrer. The stirring was continued for another 2 hours to ensure complete evaporation of acetone.

Microcapsules were then separated by filtration and washed 3 times with 50 ml of n-hexane and they were allowed to dry at room temperature.

By maintaining all process parameters constant microcapsules were formulated using three polymers namely Ethyl Cellulose, Eudragit RS and Eudragit RL in drug to polymer ratio of 1:1, 1:2, 1:3 and 1:4.

Evaluation of microcapsules

Determination of drug content

Accurately weighed quantity of microcapsules required for 100 mg of drug was dissolved in 100 ml of methanol and filtered through Whatman filter paper no. 44. Then diluted 10 ml of this solution to 100 ml and again 10 ml of this solution was diluted to 100 ml with methanol.

Absorbance was noted at 285 nm against methanol as a blank using Shimadzu UV – 150 double beam spectrophotometer. The drug content was determined form standard curve.

Determination of microencapsulation efficiency

From the drug content of microcapsules, microencapsulation efficiency was determined by formula:

$$\text{Microencapsulation Efficiency} = \frac{\text{Estimated percent drug content}}{\text{Theoretical percent drug content}} \times 100$$

Determination of various bulk properties

Bulk density

Bulk density was determined by 3 tap method, weighed quantity of prepared microcapsules was filled in

graduated cylinder. The initial volume was noted and final volume after tapping was noted.

$$\text{Bulk density} = \frac{\text{Weight of sample in gms}}{\text{Final volume after tapping}}$$

Flow properties

Frictional force in the loose powder can be measured by the angle of repose. It is calculated by following equation.

$$\theta = \text{Tan}^{-1} H/R$$

Where

θ = Angle of repose.

H = Height of cone.

R = Radius of cone

Particle size distribution [10,11]

Size distribution plays a very important role in determining the release characteristics of the microcapsules. Optical microscopy was used to determine particle size distribution.

***In – vitro* drug release**

In vitro drug release of carbamazepine was determined in USPXX rotating basket dissolution apparatus at 100 rpm and 37^{0}C using 1% SLS in distilled water as a dissolution media. Aliquots were withdrawn at an interval of 1 hour and were analyzed at 288 nm using Shimadzu UV – 150 double beam spectrophotometer.

Optimization of microcapsules

From 12 batches of microcapsules the batch that showed highest drug encapsulation and better sustained drug release effect for required period was optimized. It was studied for surface Topology, Compatibility and stability.

Surface topology

Microcapsules were scanned using Scanning Electron Microscope (JXA 840 – JAPAN). For the SEM, the microcapsules were mounted directly on to the SEM sample stub using double sided sticking tape, and coated with gold in Quick Auto Coater (JEOL Japan), with thickness of 300 mm under reduced pressure of 0.001 torr. The shape and surface characteristics of the microcapsules was observed under electron microanalyser and photographs were taken using SM 4504 camera, after magnification to 60X.

Compatibility study

FTIR spectroscopy (Shimadzu 8010) was performed to determine any interaction between drug and polymer.

Stability studies

Microcapsules were taken in crucible and placed in oven at 40^0 c for 8 weeks. They were then analyzed for drug content and drug release profile.

RESULTS AND DISCUSSION

Percent drug content and encapsulation efficiency

It was observed from the Table I that the total drug content was less than the theoretical. It may be due to loss of drug during formulation. But on the other side method showed good encapsulation efficiency. Percent drug encapsulated was found in the range of 83 – 94 %. Microcapsules prepared in 1:4 ratio of carbamazepine: ethyl cellulose was found to containing highest percent drug encapsulated (94.4%) and it is lowest in 1:1 ratio of carbamazepine: Eudragit RSPO (83.70%).

It was found that with the increase in polymer concentration the encapsulation efficiency increased which, probably, due to formation of condensed film of polymer around the dispersed drug particle.

Bulk density: It can be seen from the table II that values of bulk density are less than 1.2 gm/m^3. This indicates good flow characteristics of microcapsules.

Angle of repose: It can be observed from table III that all the batches of microcapsules have angle of repose less than 40^{0}C indicate good flow properties.

Table I: Percent drug content and encapsulation efficiency of different batches of microcapsules

Polymer	Ratio (drug: polymer)	Abs.	Conc. Mcg/ml	Drug content (mg)	% Drug contents (Pract. Yield)	Theo. Yield	Encapsulation efficiency
Ethyl Cellulose	1:1	0.376	8.56	42.80	42.80	50	85.6
	1:2	0.390	8.87	44.35	29.56	33.33	88.68
	1:3	0.407	9.26	46.30	23.15	25	92.60
	1:4	0.415	9.44	47.20	18.88	20	94.4
Eudragit RSPO	1:1	0.368	8.37	41.85	41.85	50	83.70
	1:2	0.375	8.53	42.65	28.43	33.33	85.29
	1:3	0.380	8.65	43.25	21.62	25	86.48
	1:4	0.407	9.26	46.30	18.52	20	92.60
Eudragit RL100	1:1	0.387	8.81	44.05	44.05	50	88.1
	1:2	0.390	8.87	44.35	29.56	33.33	88.68
	1:3	0.407	9.26	46.30	23.15	25	92.6
	1:4	0.410	9.33	46.65	18.66	20	93.30

Table II: Bulk density of various batches of microcapsules

Ratio Carbamazepine: polymer	Bulk density (gm/cm^3)		
	Ethyl cellulose	Eudragit RSPO	Eudragit RL 100
1:1	0.30	0.50	0.36
1:2	0.28	0.53	0.38
1:3	0.39	0.49	0.41
1:4	0.36	0.46	0.42

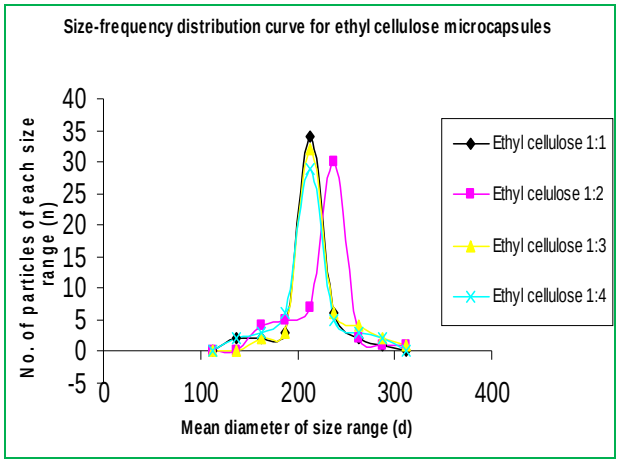
Table III: Angle of repose of various batches of microcapsules

Ratio Carbamazepine: polymer	Angle of repose (°)		
	Ethyl cellulose	Eudragit RSPO	Eudragit RL100
1:1	39.80	35.53	33.11
1:2	36.52	34.28	28.17
1:3	37.54	33.11	29.98
1:4	35.53	36.02	29.05

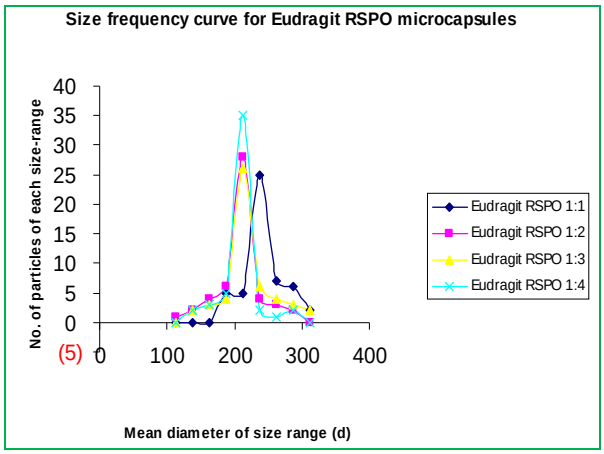
Particle size distribution: Microcapsules have a size range of 127 – 321 µm. It can be observed from the Figure 1a, 1b, 1c that microcapsules have a size – frequency distribution in range of 200 – 250 µm.

Figure 1: Size-frequency distribution curves for microcapsules prepared using various polymers in varying ratios

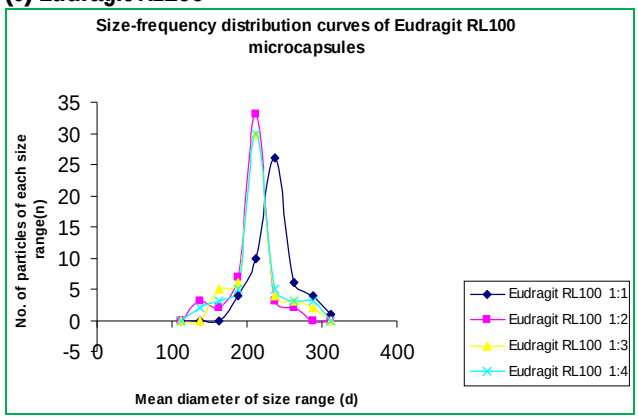
(a) Ethyl Cellulose



(b) Eudragit RSPO



(c) Eudragit RL100



The microcapsules were uniform and free flowing which may be attributed to maintenance of process parameter such as speed, stirring time, vol. of liquid paraffin and concentration of SPAN 80 constant.

***In vitro* drug release profile**

Carbamazepine is practically insoluble in water. Hence USP reported dissolution media containing 1% SLS was used. On comparing the drug release of unencapsulated drug with microcapsules drug release it was found that ethyl cellulose microcapsules (See Figure 2) in 1:1 ratio gave required drug release followed by Eudragit RL microcapsules (See Figure 3) in 1:2 ratio.

Figure 2: *In-vitro* release profile of microcapsules prepared with ethyl cellulose

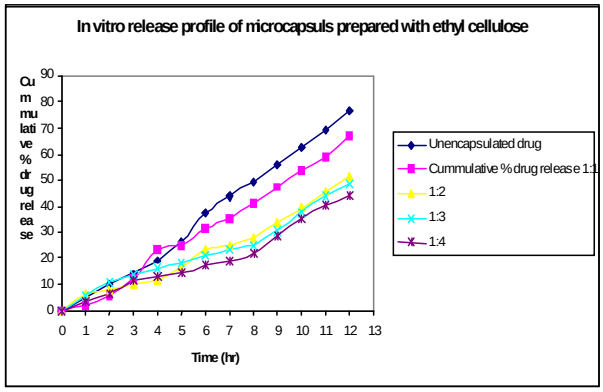
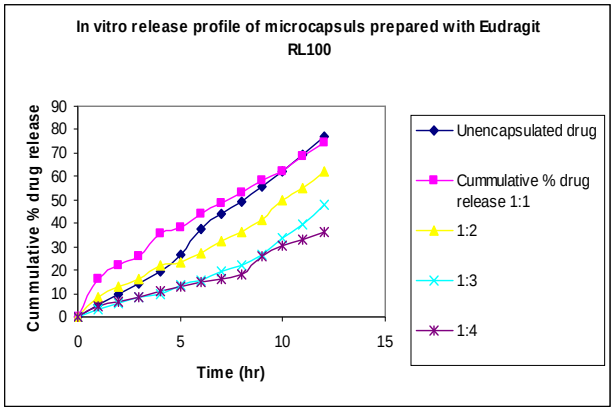
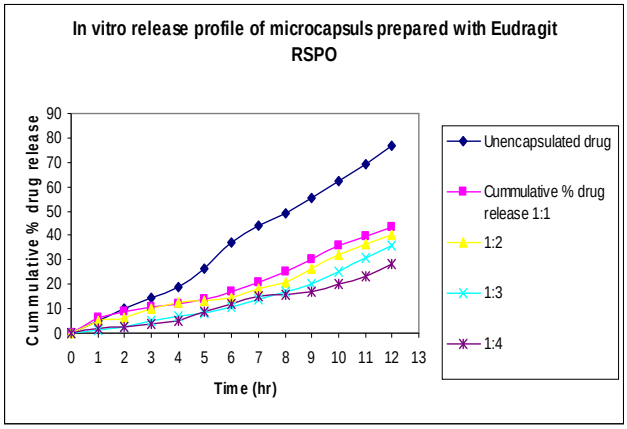


Figure 3: *In-vitro* release profile of microcapsules prepared with eudragit RL 100.



Microcapsules formulated with Eudragit RSPO (See Figure 4) showed very slow drug release as it has low permeability. Increasing the drug to polymer ratio resulted decrease in dissolution rate as a result of increased coat thickness surrounding the drug particles which increases distance traveled by the drug through the coat.

Figure 4: *In-vitro* release profile of microcapsules prepared with Eudragit RSPO



From this study, it was found that microcapsules formulated with ethyl cellulose in 1:1 ratio showed desired results hence this formulation was further studied for FT-IR Spectroscopy and SEM studies.

FT-IR Studies

Microcapsules pure drug and Ethyl cellulose were scanned (See Figures 5a, 5b, and 5c) characteristic bound at 1610, 1490 and 740 cm^{-1} due to aromatic system, bands at 1680 cm^{-1} due to – C = O of amide group. Peak at 3240 cm^{-1} due to –NH group revealed the carbamazepine structure and C-H stretching bond is shown by the bond at 2950 cm^{-1} confirmed ethyl cellulose structure.

All the characteristic bonds of carbamazepine were present in FT-IR spectrum of microcapsules. No new bonds or shifts in characteristic peaks appeared. All this indicates no interaction between drug and ethyl cellulose.

Figure 5a: FTIR Spectrum - Carbamazepine

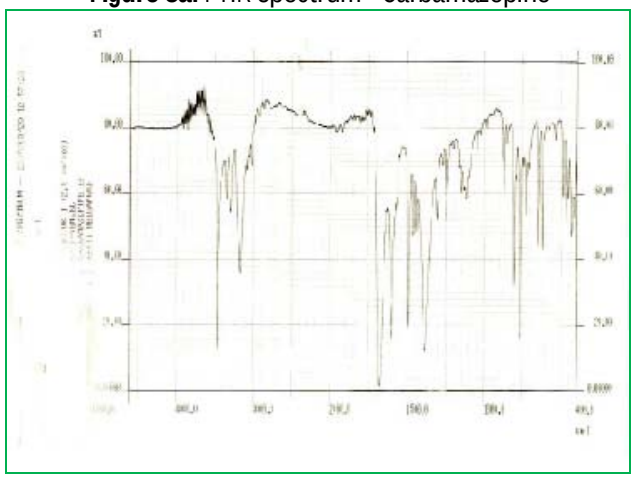


Figure 5b: FTIR Spectrum - Ethyl Cellulose

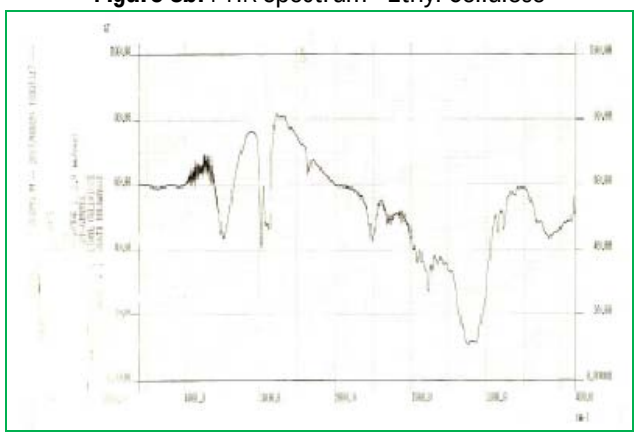
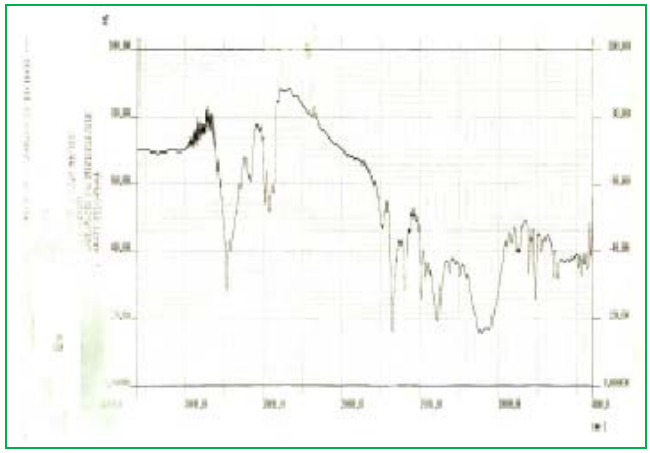


Figure 5c: FTIR Spectrum - Microcapsules



Scanning electron micrographs

Scanning Electron Micrographs of microcapsules are shown in Figure 6a and Figure 6b. The microcapsules were spherical in shape with fine pores on the surface.

Stability study

Stability study performed at 40^0C for 8 weeks was analyzed for drug content and drug release. The microcapsules were found to be stable having no change in its release profile indicates the stability of the formulation.

Figure 6(a): Scanning Electron Micrograph of optimized microcapsules at 20 x magnification.

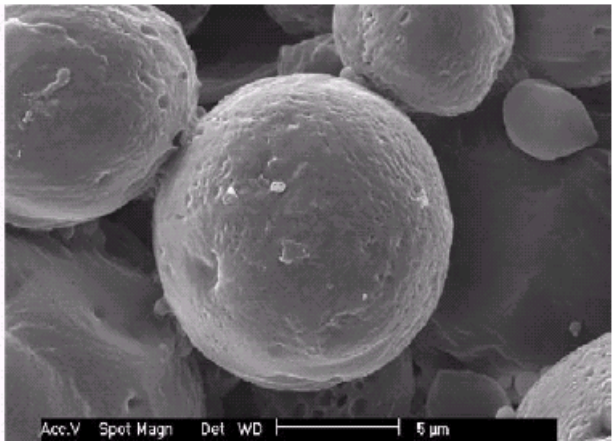
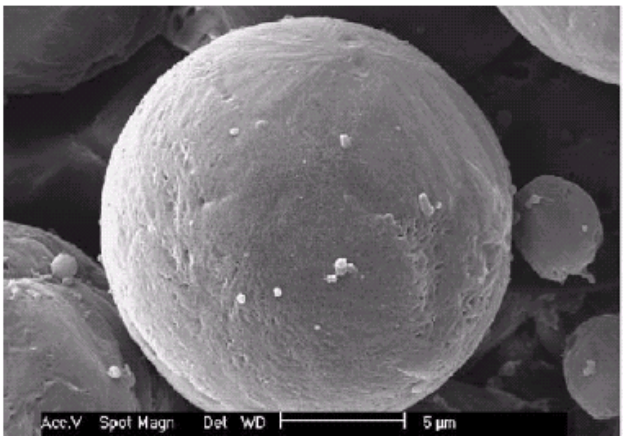


Figure 6(b): Scanning Electron Micrograph of optimized microcapsules at 60 x magnification.



CONCLUSION

Microcapsules of carbamazepine have been prepared by Emulsification-Solvent-Evaporation technique using various release retardant polymers. Among the factors studied, concentration of polymer in the formulation had an effect on the dissolution of carbamazepine and encapsulation efficiency. Of the three polymers studied, microcapsules formulated with ethyl cellulose showed good release and encapsulation efficiency followed by Eudragit RL.

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