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DESIGN AND EVALUATION OF SUSTAINED RELEASE CHITOSAN COATED PHENYLEPHRINE HYDROCHLORIDE MICROCAPSULES

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ABSTRACT

The present research work was undertaken to formulate and evaluate sustained release coated microcapsules of Phenylephrine HCl for 24 hours. Phenylephrine HCl is sympathomimetic vasoconstrictor that has been used as a nasal decongestant, having a half life of 2.5±0.5 hours and enhance frequent dosing is required to maintain therapeutics plasma concentration. Therefore, sustained release microcapsulated dosage form of Phenylephrine HCl having a release profile upto 24 hours, decrease the frequent dosing and will maintain steady state therapeutics plasma concentration which will also greatly improve patient compliance. Phenylephrine HCl was complexed with cationic resin that is Amberlite IR-120 and then coated with ethylcellulose to obtain microencapsulated resinate which will be having a release profile up to 24 hours. Chitosan coating was further given to microcapsulated resinate to increase the transit time of the dosage form in the GIT. The optimized formulation was achieved with the ratio 1:2.5 of drug-resin complex and coat/core ratio of 1:2 having 6% w/v ethylcellulose. The bioadhesive coating of chitosan was found to be optimum with 1% w/v concentration.

KEYWORDS

Phenylephrine HCl, Amberlite IR-120, Ethylcellulose, Chitosan, Microcapsules, Solvent evaporation.

INTRODUCTION

Sustained release dosage forms aimed at controlling the rate of release as well as maintaining desire drug level in the blood for long duration. Many therapeutic benefits could be gained by incorporating functions of sustained drug release into microcapsulated dosage form[1-3]. They include improvement of rate and extent of drug absorption, higher patient compliance, reduction of side effects and taste masking for bitter drugs. Microcapsulation have proved to be a successful delivery system industrially and clinically for variety of drugs for a multitude of reasons. Various methodologies have been established for production, all of which ensures that the formulation developed should perform as programmed[4,5]. Phenylephrine is a synthetic sympathomemetic agent chemically

DESIGN AND EVALUATION OF SUSTAINED RELEASE CHITOSAN COATED PHENYLEPHRINE HYDROCHLORIDE MICROCAPSULES

related to ephedrine and epinephrine indicated for the symptomatic relief of sinusitis, bronchitis and other symptoms associated with the common cold[6-9]. The action of Phenylephrine is primarily that of vasoconstriction and its effect is more long lasting than either epinephrine or ephedrine. Phenylephrine is an especially interesting candidate for oral sustained release formulation because of the current concern over the illegal diversion of other sympathomemetic compounds such as Pseudoephedrine HCl[10,11]. Therefore, the present work was aimed at studying the suitability of the formulation of sustained release Phenylephrine HCL based on coated microencapsulated drug-resin complex.

MATERIALS AND METHODS

Phenylephrine HCL was a gift sample from M/s Micro Labs, Bangalore; Amberlite IR-120 was obtained as gift sample from BPRL, Bangalore, and Ethyl cellulose was a gift sample from Karnataka Antibiotics Pvt. Ltd., Bangalore. All other chemicals used were of analytical grade.

(i) Methodology:

In the O/O method, the resin particles were suspended in 15ml of a solution of ethyl cellulose polymer (0.3, 0.6, 0.9, 1.2 gm) in acetone followed by emulsification of the phase in 100ml of liquid paraffin containing 1% w/w span 80. The resulting emulsion was maintained at 45^{o}C and agitated at 1500 rpm with a propeller stirrer until the complete evaporation of acetone was accomplished (2h). After that, the microcapsules were collected by filtration, washed with three portions of 75ml of petroleum ether and dried at 55^{o}C under the vacuum for 24 hours.

The further coating was done by technique as described by Yamada T., Onishi H. and Machida Y[12](Fig 1).

Basic technique for encapsulation

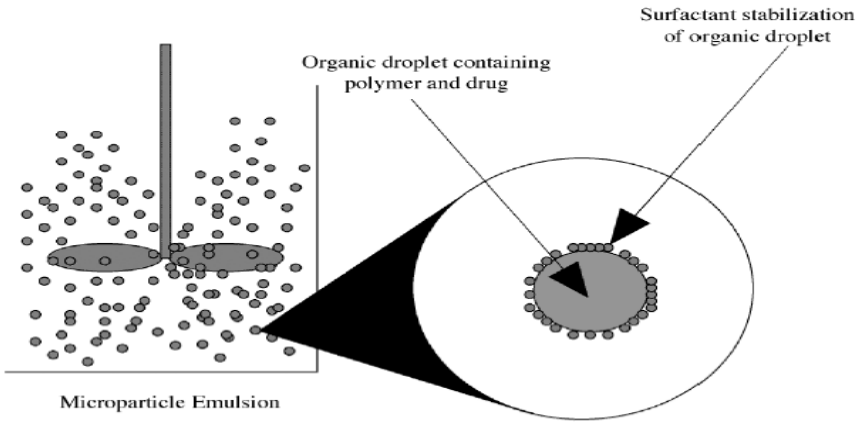

Figure 1 ***Encapsulation using oil-in manufacturing vehicle emulsion technique***

Chitosan (0.5% and 1%) was dissolved in 10ml of 2% (v/v) acetic acid aqueous solution. The selected microcapsules (coat/core ratio 1:3) was suspended in the solution, and added drop-wise to

DESIGN AND EVALUATION OF SUSTAINED RELEASE CHITOSAN COATED PHENYLEPHRINE HYDROCHLORIDE MICROCAPSULES

20ml of liquid paraffin containing sorbitan sesquioleate (SO-15) at 1% (w/v) and stirred at 600 rpm for 30minute. The suspension was added drop-wise to 500ml of double solvent layer of n-hexane/ 1M NaOH (2:3 v/v) and stirred at 300rpm. After one minute of dropping, liquid paraffin was washed off in the upper layer (n- hexane) and the Chitosan was precipitated in 1M NaOH aqueous layer, were collected by filtration and washed with 500ml of deionized water, and dried in a desiccator in vacuum at room temperature to produce CChotosan microcapsules (Chi-MC).

(ii) Drug Content in Microcapsules:

The phenylephrine HCL content of the microcapsules was determined in duplicate for each batch formulation after dissolving the polymer coat of the microcapsules (100mg dry weight) in 10ml of acetone. The remaining resin particles were then filtered, then stirred in 50ml of pH1.2 buffer solution up to 3hr. and then aliquot (0.5 ml) was taken, and filtered. The filtrate, following suitable dilution (up to 10ml) was assayed spectrophotometrically at 273.5nm.

The phenylephrine HCL content of the Chitosan-MC was determined in duplicate for each batch formulation after dissolving the polymer coat (Chitosan) of the Chi-MC (100mg dry weight) in 5% v/v acetic acid aqueous solution and later ethyl cellulose coat with 10ml of acetone. The remaining resin particles were then filtered, then stirred in 50ml of pH1.2 buffer solution up to 3hr. and then aliquot (0.5 ml) was taken, and filtered. The filtrate, following suitable dilution (upto 10ml) was assayed spectrophotometrically at 273.5nm.

The Percentage Yield, Drug loading, Entrapment Efficiency were calculated by following formula:

$$\text{Microcapsules yield (\%)} = \frac{\text{Weight of microcapsules}}{\text{Weight of polymer and drug fed initially}} * 100$$

$$\text{Drug loading content (\%)} = \frac{\text{Weight of drug in microcapsules}}{\text{Weight of microcapsules}} * 100$$

$$\text{Microencapsulation efficiency (\%)} = \frac{\text{Weight of drug in microcapsules}}{\text{Weight of drug fed initially}} * 100$$

(iii) Scanning Electron Microscopy (SEM):

The surface of microcapsules was examined by scanning electron microscopy. Microspheres were dusted onto double sided carbon tape, which was placed onto a cylindrical sample carrier. The samples were coated with Au-Pd mixture under vacuum with a sputter coater to thickness of 50 nm. The samples were imaged using 5 kV electron beam.

(iv) In vitro drug release study from microcapsule:

In vitro release of Phenylephrine HCL from microcapsules was monitored in 900ml of simulated gastric fluid (SGF; pH 1.2) and

DESIGN AND EVALUATION OF SUSTAINED RELEASE CHITOSAN COATED PHENYLEPHRINE HYDROCHLORIDE MICROCAPSULES

simulated intestinal fluid (SIF; pH 6.8) at 37 ± 0.5^{0}C using a programmable dissolution tester (paddle type) at 50 rpm, respectively. The dissolution was continuous up to 24 hours. Aliquots (3ml) were withdrawn at the predetermined time and were replenished immediately with the same volume of the fresh medium. The aliquots, following suitable dilution (10ml), were assayed spectrophotometrically at 273.5nm. From this percentage drug release was calculated and this was plotted against function of time to find out the pattern of drug release.

Then the best formulation was selected based on particle size, % yield, microencapsulation efficiency, drug loading, and morphology and drug release.

(v) In vitro mucoadhesive study:

The in vitro mucoadhesive test was carried out using a small intestine isolated from rats. Fasted rats (300-350g) were scarified, and then flushed with saline. Five-centimeter segments of jejunum were everted using a glass rod. Ligatures were placed at both ends of the segments. Chi-MC were scatters uniformly on the everted sac from the position of 2 cm above. Then the sac is suspended in a 10ml tube containing 8 ml pH1.2 buffer solution by the wire, to immerse in the buffer solution completely. The sac was incubated at 37^{o}C and agitated horizontally. The sac was taken out of the medium after immersion for 1, 2, 4, 6 and 8 hr, immediately repositioned as before in a similar tube containing 8 ml of flesh buffer solution and unbound Chi-MC were counted.

The adhering percentage was presented by the following equation:

$$\text{Adhering} = \frac{50 - \Sigma_{t=0}\, N_t}{50} * 100$$

Where N_t is the number of unbound Chi-MC at the time t after incubation.

RESULTS AND DISCUSSIONS

Accordingly to develop a suitable drug delivery system of Phenylephrine HCL, it was first subjected to theoretical assay studies using melting point and its characteristics U.V. and I.R. spectra. It was found that the drug was conforming to pharmacopoeial standards with respect to melting point, wavelength of maximum absorption (λ_{max}) and the characteristic IR peak.

Having ensured the purity of the drug and verified λ_{max} of the drug in appropriate solvent, the standard calibration curve was prepared, which exhibits linear relationship between drug concentration and UV absorbance both in the Distilled water, pH 1.2 and pH 6.8 phosphate buffers in the Beer's range of 4 to 28 µg/ ml.

DESIGN AND EVALUATION OF SUSTAINED RELEASE CHITOSAN COATED PHENYLEPHRINE HYDROCHLORIDE MICROCAPSULES

The aim of the research was to prepare microcapsules by solvent evaporation method by keeping the coat/core ratio and the volume of organic disperse phase constant, the concentration of the ethylcellulose was varied from 2%, 4%, 6% and 8% w/v. the resinate encapsulation efficiency of the microcapsules was found the to be influenced by the concentration of the polymer. Since in the present study, the maximum drug-loaded resinate was used for encapsulation. The encapsulation efficiency and drug loading appeared to depend on the viscosity of the disperse phase. At the lower EC concentration, the microcapsules formed a very homogeneous population, the mean particle size being fairly similar to that resin particle. At high EC concentration, the mean particles size of the microcapsules found fairly bigger because of the little aggregation of the resin particles. The master batch formulae and their characteristics are described in (Table 1).

The releases profiles of the drug from resinate and coated resinate prepared using different concentration of the polymer. The drug release from the uncoated drug resinate was rapid and drug release rate was found to be > 99% in 3 hours. Although the drug release from the Amberlite IR-120 resin complex was found to be independent of the pH. The release of the drug from the microcapsules was slower than that from the uncoated resinate, the retardation of the drug release was influenced by formulation parameters. The observation could be corroborate by the morphology of the microcapsules and the complex drug release mechanism involving penetration of counter ions into the microcapsules, ion exchange, and subsequent diffusion of the free drug from the microcapsules. The amount of polymer that not only caused uniform coating but also increased the coating thickness of the microcapsules. This increased the path length through which the drug molecules had to diffuse and the time required to transverse the membrane and hence made the drug release slower from the microcapsules. SEM of the formulations was almost spherical in nature with slight smooth surface morphology (Fig 2).

Table 1
Master batch formulae and their characterization

Product code	Conc. of ethyl cellulose used (%)	% Yield	Weight of MC (in mg)	Drug content (mg)	% drug loading	Average diameter (µm)
EC2	2	88.77	799.6	91.68	11.46	434.5
EC4	4	99.44	1792.5	323.58	18.05	526.38
EC6	6	94.54	3152.8	561.36	17.80	538.21
EC8	8	97.22	3505.2	684.56	19.52	545.93
CM1	-	86.62	173.25	22.41	12.93	-
CM2	-	91.17	91.17	50.93	13.96	-

DESIGN AND EVALUATION OF SUSTAINED RELEASE CHITOSAN COATED PHENYLEPHRINE HYDROCHLORIDE MICROCAPSULES

Scanning electron microscopy (SEM)

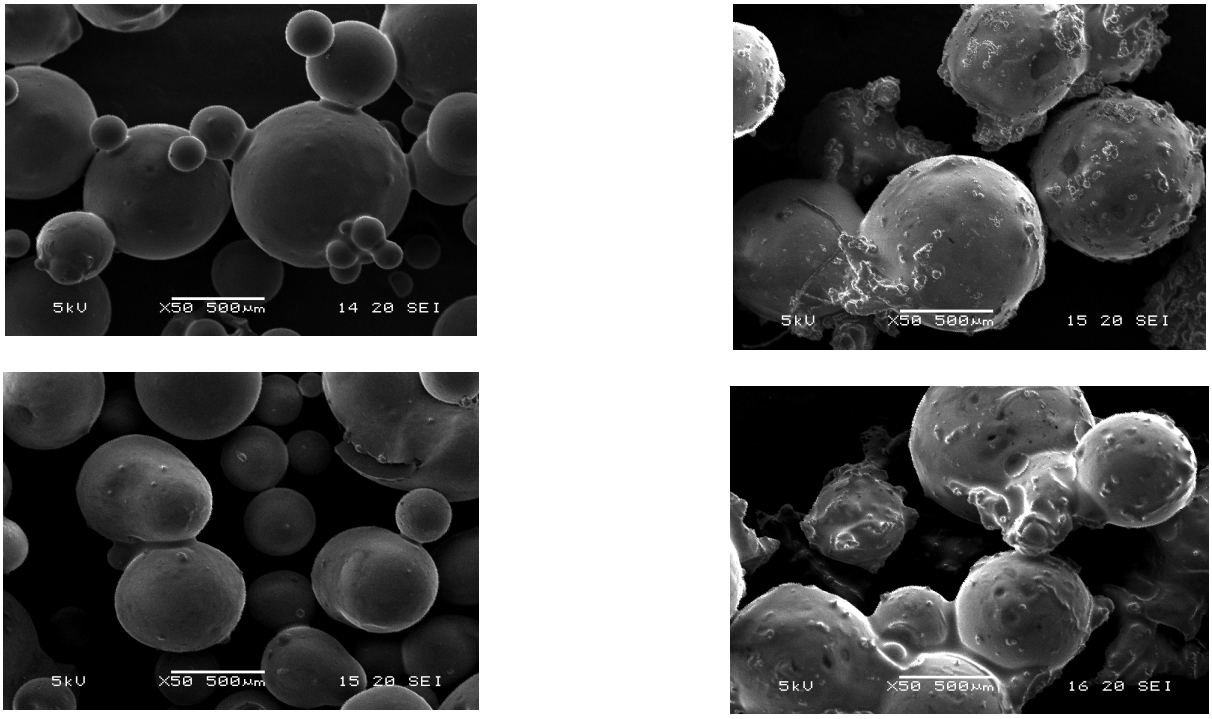

Figure 2 *SEM (Scanning Electron Microscopy) of EC2, EC4, EC6, EC8*

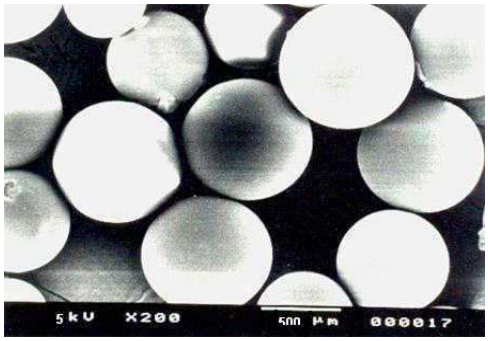

Figure 3 *SEM of microcapsules after in vitro release study*

DESIGN AND EVALUATION OF SUSTAINED RELEASE CHITOSAN COATED PHENYLEPHRINE HYDROCHLORIDE MICROCAPSULES

The release profiles further indicated that the drug release from the microencapsulated resinates was independent of pH.Interestingly, the surface of the microcapsules after the dissolution studies was found to be unaltered (Fig 3).This indicates that the EC coating provided sufficient resistance to prevent the rapture of the coating film that from rehydration and swelling of the dried resinate, hence that the process does not require any impregnating agent.

The concentration of the Chitosan was varied from 0.5 and 1 % w/v in 2% v/v acetic acid aqueous solution. The encapsulation efficiency of the microcapsules was found to be influenced by the concentration of the polymer. The release profiles of the different formulations prepared using different concentration of the polymer appear in Fig 4 and Fig 5.

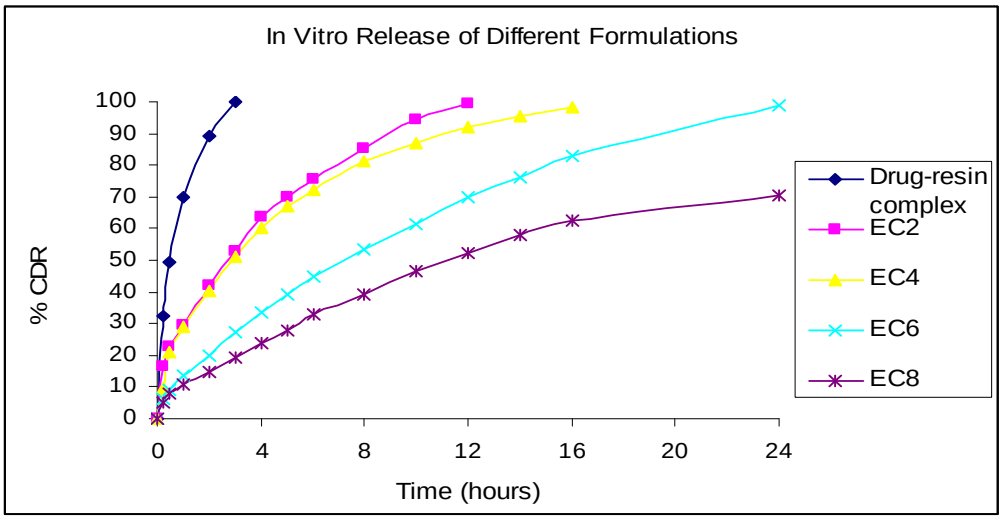

Figure 4 ***In vitro releases*** **of different formulations**

DESIGN AND EVALUATION OF SUSTAINED RELEASE CHITOSAN COATED PHENYLEPHRINE HYDROCHLORIDE MICROCAPSULES

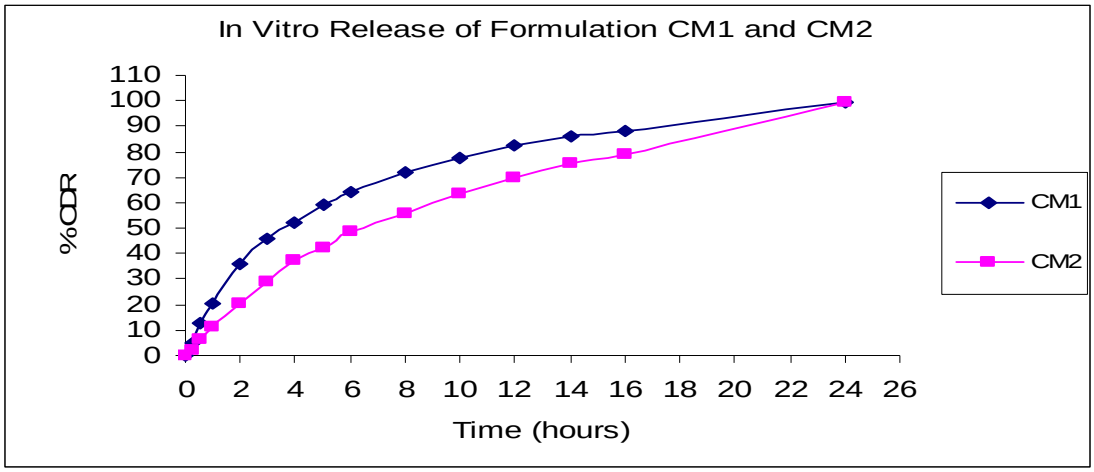

Figure 5 ***In vitro release of formulation CM1 and CM2***

The adhesion profile of the Chi-MC to the intestinal mucosa is shown in Fig 6**.**

***In vitro* Mucoadhesion study**

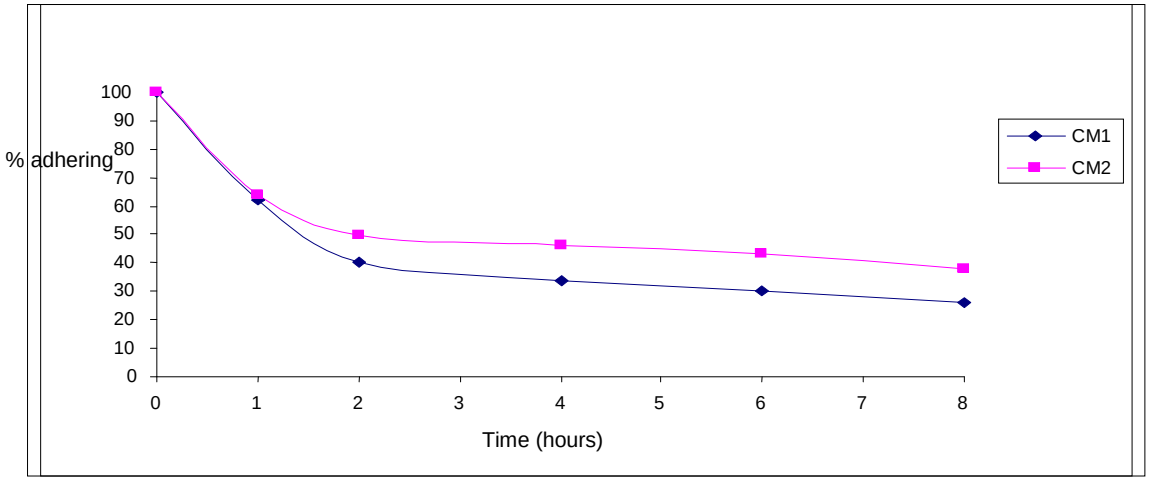

Figure 6 ***In vitro Mucoadhesion to the rat small intestinal Mucosa***

DESIGN AND EVALUATION OF SUSTAINED RELEASE CHITOSAN COATED PHENYLEPHRINE HYDROCHLORIDE MICROCAPSULES

Chi-MC exhibited quick adhesion to the mucosa. The decrease in ratio of adhering Chi-MC after the start of the test was considered due to dissolution and exfoliation of the part of the mucosa. This suggests that Chi-MC have good adhesion to the intestinal mucosa up to 8 hours. The 26% and 37% of Chi-MC adhered to rat intestinal mucosa from formulation CM1 and CM2 respectively up to 8 hours.The exchange of the resin from the uncoated resinate was found to follow the particle diffusion process in accordance the kinetic model. Drug release from the coated resinates and Chi-MC has also been reported to follow the particle diffusion process. However, the phenylephrine HCl release from the coated resinates and microcapsules were found to deviate from the particle diffusion mechanism. Hence, the data were fitted into the Higuchi and Korsmeyer-Peppas. In Peppas equation $Mt/M\alpha = at^n$, where a, is constant incorporating structural and geometric chatersticis of the dosage form, n is the release exponent, indicative of the drug release mechanism. In starting of drug release, it was observed that n is near to 0.45, this indicates that drug release is Fickian diffusion and later n is between 0.45-0.89 then the release is non fickian diffusion.

Fitting the release data into the Higuchi equation yielded comparable linearity for all the microcapsules. Although inconclusive without further investigation, the present study indicated that release of phenylephrine Hcl from the MC and Chi-MC obeyed a diffusion-controlled process. The release rate pattern was found to follow mixed order release kinetics having both dissolution and diffusion release rate with respect to time, i.e. from 0-10 hours (it was found to follow first order), and from 10-24 hours (Zero order) release rate.

CONCLUSION

The study revealed uniformly bioadhesive polymer coated resinate-loaded Phenylephrine HCL microcapsules can be prepared by solvent-evaporation method through proper adjustment of formulation parameters. The microcapsules having a reasonably resinate loading effienciency, effectively control the release of a relevant amount of the active drug over a 24 hour period with good adhesion of microcapsules in the gastro intestinal tract and release the drug, independent of the pH of the dissolution medium. The present study indicated that release of drug from the coated microcapsules obeyed dissolution diffusion controlled process and mixed order release rate.

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DESIGN AND EVALUATION OF SUSTAINED RELEASE CHITOSAN COATED PHENYLEPHRINE HYDROCHLORIDE MICROCAPSULES

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