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Research Article

FORMULATION AND OPTIMIZATION OF VERAPAMIL HYDROCHLORIDE MICROCAPSULES

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ABSTRACT

Verapamil hydrochloride microcapsules prepared with sodium alginate, carbopol and magnesium start in different ratios of polymers with the drug by the iconic Gelation Technique and the prepared microcapsules were evaluated for size range, drug content, drug release profiles, and kinetics of drug release. All the microcapsules were discrete, free flowing, and reproducible with respect to size distribution and drug content. The maximum percentage of the microcapsules belonged to the size range of 500µm. Drug release from the microcapsules (MC1 andMC2) was 94-97 % in first 6 hours, with the initial burst of nearly 50% within one hour. Drug release from microcapsules (MC3 and MC4) was 90-95% and sustained up to 8 h with initial burst of 50-54 % in first 6 h, resulted with increase in cross-linking time for 5-6 hours, Drug release from microcapsules (MC5 and MC6) sustained the drug release up-to 12 hours, with an initial burst release of 35-37 % within first one hour with increase in cross-linking time for 5-6 hours and addition of magnesium stearate (2-4 %w/w) and cumulative release of over 90-93% and indicated that the drug release from the microcapsules was found to be slow and spread over an extended drug release. Based on r^2 values the drug release followed first order kinetics and diffusion mechanism. Drug release from the microcapsules depends on the composition of the coat, cross linking time and also influenced by magnesium stearate.

Keywords: Verapamil Hydrochloride, Calcium channel blocker, Hypertension, Angina pectoris, Cardiac arrhythmias, Microcapsules and Sustained release

INTRODUCTION

Microencapsulation is a rapidly expanding technology. As a process, it is a means of applying a thin coating to small particles of solids or droplets of liquids[1]. The Applications of microencapsulation might well include sustained-release or prolonged action medications etc. Microencapsulation is a topic of current interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of the drug. However, prior to the advent of improved alternate methods, drug delivery systems were considered only as a means of getting the drug into the patient's body. Microencapsulating is receiving considerable attention fundamentally, developmentally and commercially. It is a rapidly expanding technology. Microencapsulation has been used in the pharmaceutical industry for the conversion of liquids to solids, taste masking of bitter drugs, acquiring prolonged or sustained release, and reducing gastric irritation and environmental. The Microencapsulation carrier system made from various polymers has

attracted considerable attention for several years in the sustained drug delivery. Recently, dosage form that can precisely control the release rates and target drugs to a specific body site has made an enormous impact in the formulation and development of novel drug delivery systems.

Verapamil Hydrochloride (VPH) which is widely used in the treatment of hypertension, angina pectoris and cardiac arrhythmias VPH are formulated as sustained release microcapsules by using carpal and sodium alginate which is a non biodegradable and a biocompatible polymer. It is extensively used as an encapsulating material for sustain release formulations. Microencapsulation may improve the absorption of a drug and reduce the side effects such as irritation to the gastrointestinal mucosa. The present study was to formulate the sustained release microcapsules of VPH. VPH was suitable candidate for sustained release microcapsules since it has low oral bioavailability[2] of 22± 8% and short biological half-life (4.0±1.5 hr).

MATERIALS & METHODS

Materials

Verapamil Hydrochloride was obtained as a gift sample from Alkem laboratories Ltd (Mumbai, India), Carbopal-934p and Sodium alginate was obtained from Colorcon Asia Pvt (Mumbai, India), Magnesium stearate were purchased from Loba chemicals, Mumbai. All other reagents used were of analytical grade.

Preparation of Microcapsules [3,4]

VPH Microcapsules were prepared by the orifice ionic gelation method with polymer combinations such as, carbopol and sodium alginate in ratios of 1:3 w/w and 3:1w/w as shown in Table 1. The polymer mixture was dissolved in distilled water (32 ml) to form a homogenous polymer solution. The core material, VPH was added to the polymer solution and mixed thoroughly to form a viscous dispersion. The resulting dispersion was added drop wise into 250ml calcium chloride solution (10%w/v) through a syringe fitted with a needle of 21 gauges. The added droplets were retained in the calcium chloride solution for 3 h to complete the curing reaction and to produce spherical rigid microcapsule. The microcapsules were collected by decantation and the product thus produced was washed repeatedly with water and dried at 45^0C for 8 h in hot air oven.

EVALUATION OF MICROCAPSULES

Particle size analysis [5]:

Particle size analysis was done by sieving method using Indian standard sieves ≠ 10, 12, 16, 20, 22, 40, 44. Average particle size was calculated using the formula

$$d_{avg} = \Sigma dn / \Sigma n$$

Where n is frequency weight and d is the mean diameter

Drug content[6]:

Drug loaded microcapsules (equivalent to 120mg of VPH) was initially triturated and stirred with 3 ml of sodium citrate solution until a complete dissolution. Methanol (15 ml) was added to the above solution to get the solubilized calcium alginate and further solubilized VPH. The solution was filtered through Whatmann filter paper No.42 and assayed for drug content by a UV - spectrophotometer (Analytical) at 278 nm. (Table2)

Encapsulation Efficiency [7]:

Microencapsulation efficiency was calculated using the formula:

Microencapsulation Efficiency (%) = (Estimated percent drug content/ Theoretical percent drug content) * 100. (Table2)

Wall thickness[8]:

Wall thickness of microcapsules was determined by the method of Luv et. *al.* using the equation,

$H = r (1-p) d_1 /3[pd_2 + (1-p)d_1]$,

Where H is the wall thickness, r is the arithmetic mean radius of microcapsules, d_1 and d_2 are the density of the core and coat materials respectively, and p is the proportion of the microcapsules.

SEM analysis:

The microcapsules were observed under a Scanning Electron Microscope (SEM) (Philips electronics N.V. XL 20 series). For SEM, the microcapsules were mounted directly onto the SEM sample stub, using a double sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).(Fig1)

In-vitro drug release studies:

Release of VPH from the microcapsules was studied in phosphate buffer of pH 7.4 (900 ml) maintained at 37 ± 0.5^0c using a USP paddle type dissolution test apparatus (Electro lab) and stirred at 100 rpm. A sample of microcapsules equivalent to 120 mg of VPH was used in each test. They were filled in empty capsule shells and placed in the apparatus. Samples (5 ml) were withdrawn at specific time intervals and

drug content was determined by UV- visible spectrophotometer (T70 U Spectrophotometer analytical model) at 278nm.The release studies was conducted in triplicate.

RESULTS AND DISCUSSION

All the microcapsules were found to be discrete, spherical and free flowing. The size could be separated and more uniform size of capsules could rapidly be obtained. The drug content ranged from 30-40 %. The results showed that the encapsulation efficiency increases with increase in alginate concentration and also the maximum efficiency with the presence of magnesium stearate. The average particle size was found to be 500µm. shown in Fig1. SEM photographs indicated that the microcapsules are discrete, nearly spherical and covered with a continuous coating of polymer.

The release of drug from various formulations was from 12 hrs and more as shown in Figure-2. Drug releases from the microcapsules were studied in phosphate buffer pH 7.4 for a period 12 hrs. Drug release from the microcapsules (MC1 andMC2) was 94-97 % in first 6 hours, with the initial burst of nearly 50% within one hour. Drug release from microcapsules (MC3 and MC4) was 90-95% and sustained up to 8 h with initial burst of 50-54 % in first 6 h, resulted with increase in cross-linking time for 5-6 hours, Drug release from microcapsules (MC5 and MC6) sustained the drug release up-to 12 hours, with an initial burst release of 35-37 % within first one hour with increase in cross-linking time for 5-6 hours and addition of magnesium stearate (2-4 %w/w) and cumulative release of over 90-93% and indicated that the drug release from the microcapsules was found to be slow and spread over an extended drug release. Based on r^2 values (Table3) the drug release followed first order kinetics and diffusion mechanism. Drug release from the microcapsules depends on the composition of the coat, cross linking time and also influenced by magnesium stearate.

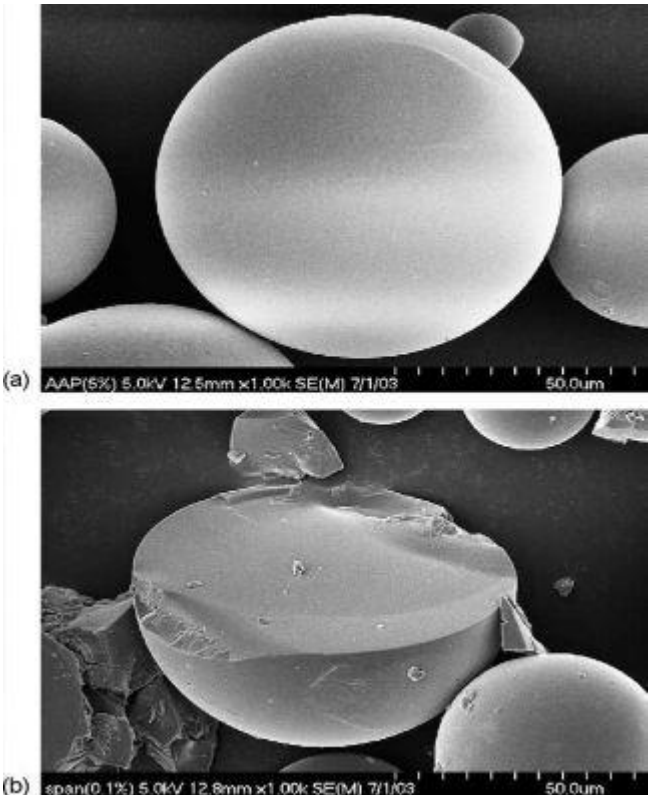

Fig-1: Morphology of the VPH microsphere: The surface (a) and the inside (b) of the microsphere.

Table-1: Composition of microcapsules.

Formulation Code	VPH(mg)	Sodium alginate Carbopal	Magnesium stearate(mg)
MC1	120	1:1	----
MC2	120	3:1	----
MC3	120	1:1	----
MC4	120	3:1	----
MC5	120	1:1	40
MC6	120	3:1	80

Table-2: Evaluation of microcapsules.

Formulation Code	Mean% drug content ±S.D.	E.E (%)	T_{90}%(hr)	Cumulative % drug release in12hr
MC1	30.13±0.512	45.07	4.30	96.67±0.512
MC2	34.02±0.231	52.31	4.93	97.12±0.321
MC3	35.98±0.563	56.07	8.07	96.10±0.413
MC4	38.184±0.276	59.58	8.95	95.32±0.375
MC5	40.23±0.651	66.93	9.70	90.31±0.437
MC6	45.21±0.434	75.43	11.65	93.12±0.352

- All are average of three determinations.

Table-3: *In-vitro* drug release kinetic studies of microcapsules

Formulation Code	Zero order (r^2)	First order (r^2)	Higuchi (r^2)
MC1	0.958	0.993	0.990
MC2	0.973	0.993	0.994
MC3	0.935	0.985	0.983
MC4	0.938	0.978	0.987
MC5	0.994	0.997	0.986
MC6	0.949	0.985	0.982

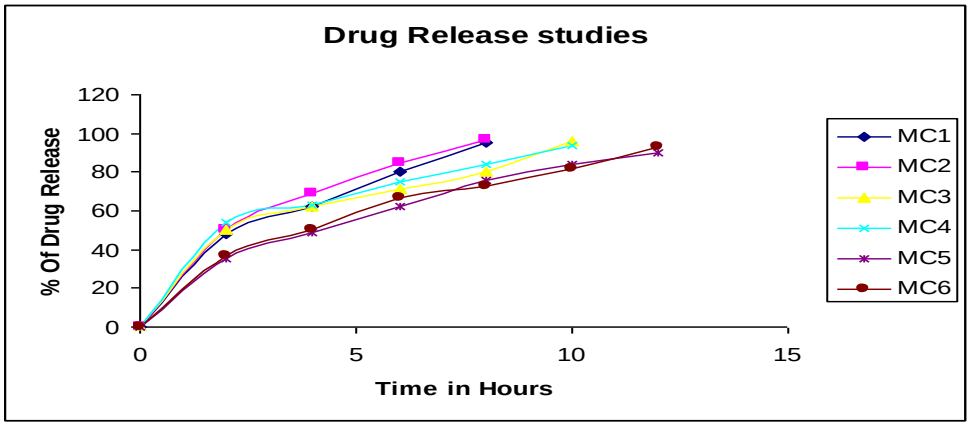

Fig. 2: Drug release data of selected six formulations

CONCLUSION

Sustained release VPH microcapsules could be formulated by using sodium alginate, carpobol and magnesium stearate as a release retardant by ion tropic gelation technique. The microcapsules of all the formulated batches were spherical, discrete and free flowing. The drug content was found to be uniform. With increasing concentration of magnesium stearate and crosslink time decreasing the drug release and it followed by first order kinetics and diffusion mechanism.

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