
Microencapsulation of Verapamil Hydrochloride by Ionotropic Gelation Technique

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Micropellets of verapamil hydrochloride were formulated by ionotropic gelation technique using sodium alginate, hydroxypropylmethylcellulose and hydroxypropylcellulose. Prepared micropellets were evaluated for flow behavior, drug entrapment efficiency, *in vitro* dissolution and stability studies, including scanning electron microscopy and optical microscopy. Of the nine formulations prepared and evaluated formulations F3, F6 and F9 were found to show satisfactory results. The release of the drug from the micropellets was found to be following non-Fickian diffusion; Drug diffusion coefficient and correlation coefficient were also assessed using various mathematical models. From the study it was concluded that, prolonged release verapamil hydrochloride micropellets could be achieved with success using ionotropic gelation technique.

Verapamil hydrochloride is a calcium channel blocker used in the treatment of hypertension, angina pectoris, certain cardiac arrhythmia and obstructive cardiomyopathies¹. It has a short half-life of 4 h¹. It also causes gastric irritation on sudden release². It is usually administered as conventional tablets containing 40-120 mg, 3 times a day. Due to its ready solubility in water and shorter half-life, the drug is an ideal choice for prolonged release formulation. Drug requires enough dosing by oral route due to its inherent short half-life; prolonged release formulation administration will lead to reduction of dosing frequency and in contrary improves patient compliance. It deserves merit to which there is increase in bioavailability in spite of drug undergoing substantial first pass metabolism³. The aim of the present study is to develop a suitable microparticulate system of verapamil hydrochloride for prolonged release delivery system. In the proposed method of ionotropic gelation technique, strong spherical beads with a narrow particle size distribution and low friability could be prepared with high yield and a drug content approaching 98 percent.

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MATERIALS AND METHODS

Verapamil hydrochloride was obtained as a gift sample from Nicholas Piramal India Ltd., Mumbai. Hydroxypropylcellulose (HPC) was purchased from Across Organics, New Jersey, USA. Hydroxypropylmethylcellulose (HPMC) from Colorcol, U.K., Sodium alginate and calcium chloride were procured from S. D. Fine Chemicals Ltd., Mumbai.

Preparation of micropellets:

The micropellets of verapamil hydrochloride were prepared by using ionotropic gelation technique. In this method weighed quantity of verapamil hydrochloride was added to 50 ml sodium alginate solution and thoroughly mixed at 500 rpm. Resultant solution was extruded drop wise with the help of syringe and needle into 100 ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 min micropellets were separated, washed with water and dried at 70° for 6 h in an oven⁴.

Three sets of micropellets were prepared. In the first set micropellets of verapamil hydrochloride were prepared

TABLE 1: COMPOSITION AND PHYSICAL CHARACTERISTICS OF THE MICROPELLETES.

Formulation Code	Sodium Alginate % (w/v)	Calcium Chloride % (w/v)	HPMC % (w/v)	HPC % (w/v)*	Drug * Entrapment Efficiency [%]	Angle of Repose * θ
F1	2	4	-	-	76.5	35° 30'
F2	3	5	-	-	78.7	33° 10'
F3	4	6	-	-	85.1	27° 40'
F4	2	4	1	-	85.5	32° 20'
F5	3	5	1.5	-	93.6	28° 20'
F6	4	6	2	-	97.8	24° 10'
F7	2	4	-	2	80.0	30° 30'
F8	3	5	-	3	87.2	28° 10'
F9	4	6	-	4	93.5	25° 40'

*Based on dry polymer weight, each formulation uses 480 mg of Verapamil hydrochloride # Values are mean/average of triplicates

using only sodium alginate in different concentrations. In the second set, micropellets of the drug were prepared in a combination of coating polymers like hydroxypropylmethylcellulose and sodium alginate. In the third set, micropellets of the drug were prepared using a combination of polymers like hydroxy propyl cellulose and sodium alginate. The detailed compositions of various formulations prepared were mentioned in Table 1.

Drug entrapment efficiency:

Accurately weighed micropellets equivalent to 100 mg were suspended in 100 ml of simulated intestinal fluid of pH 7.2±0.1 and kept for 24 h. Next day it was stirred for 5 min and filtered. After suitable dilution, verapamil hydrochloride content in the filtrate was analyzed spectrophotometrically at 278 nm using a Shimadzu 1201 UV/Vis spectrophotometer⁴.

Flow property:

Angle of repose method was employed to assess the flowability. Micropellets were allowed to fall freely through a funnel fixed at 1 cm above the horizontal flat surface until the apex of conical pile just touched the tip of the funnel. The angle of repose (θ) was determined by the formula, $\theta = \tan^{-1} (h/r)$; h=cone height of micropellets; r=radius of the circular base formed by the micropellets on the ground⁵.

In vitro release studies:

Dissolution studies were carried out in triplicate for all the formulations, employing USP XXIII apparatus (basket method) at 37±0.5° rotated at constant speed of 50 rpm using acid buffer (pH 1.2) and phosphate buffer (pH 7.2) as the dissolution medium. An aliquot of the sample was periodically withdrawn at suitable time intervals and the volume was replaced with fresh dissolution medium. The samples were analyzed spectrophotometrically at 278 nm.

Kinetics of drug release:

In order to understand the mechanism and kinetics of drug release, the drug release data of the *in-vitro* dissolution study were analyzed with various kinetic equations like zero order (% release Vs time), first order (log % retained Vs time) and Korsmeyer and Peppas equation (m/m_{∞} Vs t^n). Coefficient of correlation [r] values were calculated for the linear curves obtained by regression analysis of the above plots.

Scanning electron microscopy (SEM) analysis:

The micropellets were observed under SEM [model JSM 35CF, Jeol, Japan] at 15 kV by mounting sample on the aluminum stubs having double adhesive tape and subsequent evaporation of gold palladium alloy in the ion sput-

TABLE. 2: *IN VITRO* RELEASE KINETIC DATA OF MICROPELLETS

Formulation code	Cum percent Drug Released # [%]	Correlation Coefficient (r)		Korsmeyer and Peppas's	
		First order	Zero order	n	r
F1	96.86	0.9803	0.9773	0.4386	0.9800
F2	95.39	0.9824	0.9789	0.4669	0.9801
F3	84.83	0.9509	0.9245	0.5716	0.9034
F4	86.39	0.9433	0.9192	0.5181	0.9178
F5	74.13	0.9849	0.9737	0.8165	0.9603
F6	66.75	0.9662	0.9488	0.5808	0.9977
F7	89.23	0.9936	0.9679	0.7812	0.9394
F8	80.21	0.9917	0.9743	0.6786	0.9520
F9	72.62	0.9898	0.9705	0.7308	0.9432

n- Diffusion exponent related to mechanism of drug release, according to equation, $m_t/m_\infty = kt^n$, r- correlation coefficient and #- Values expressed as mean of triplicates, obtained at the end of 8 h.

ter unit. The microphotographs of suitable magnifications were obtained for surface photography.

Particle size analysis:

Samples of micropellets were analyzed for particle size by optical microscopy. The Olympus Model (SZX-12) having resolution of 30X was used for this purpose. The instrument was calibrated were in 1 unit of eyepiece micrometer was equal to 1/30 mm (33.33 μm). All the three dimensions (lxbxh) of the micropellets were measured⁶.

Accelerated stability studies:

Stability studies were performed according to WHO guidelines. The formulations were stored in oven at 37±1° and 60±1° for a period of 6 W. The samples were analyzed for drug content every week by spectrophotometer at 278 nm⁷. Compatibility of drug with the excipients was determined by IR spectroscopy using a Shimadzu FTIR -8000 model IR spectrometer.

RESULTS AND DISCUSSION

Chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for micropellets of verapamil hydrochloride. From the prelimi-

nary studies it was observed that with the increase in speed of rotation of calcium chloride (counter-ion) solution, the

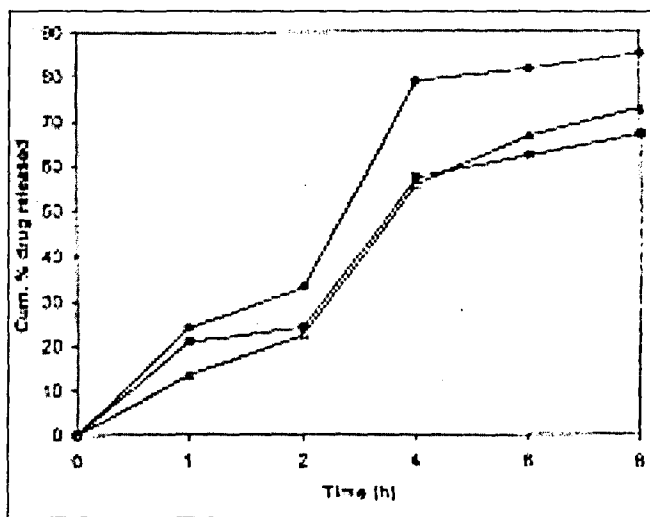
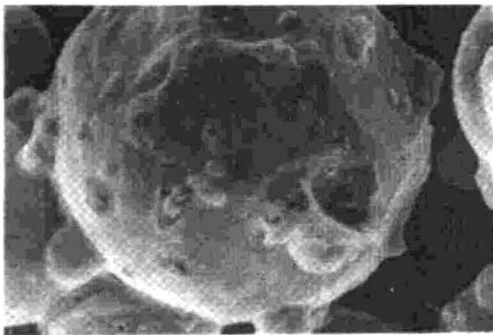
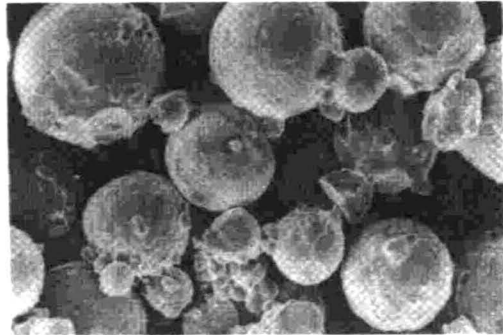


Fig.1: Plots of cumulative % drug released V/s. time for formulations F3, F6 and F9.

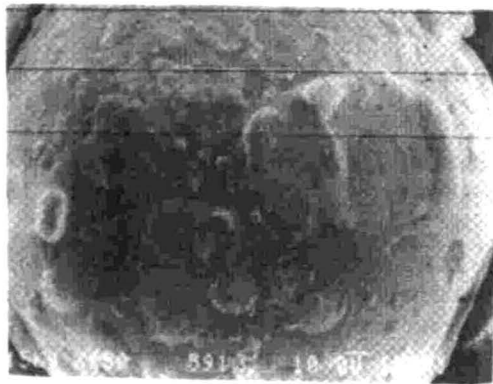
In vitro dissolution profiles of verapamil hydrochloride containing sodium alginate alone-F3 [□], sod alginate with HPMC-F6 (△) and sod alginate with HPC-F9 [○].



a



b



c



d

Fig. 2: Scanning Electron Microscopy (SEM) and photomicrographs of formulations

2a, 2b and 2c are the SEM of formulations F3, F6 and F9 at 3000X. Gold-palladium alloy of 120° A knoss was coated on the sample using sputter coating unit. 2d is the photomicrograph of formulation F6. Olympus model [SZX-12] having a resolution of 30X was used.

pellet size decreased. Also it was found that with the increase in harvesting time, the pellets formed in turn decreased the drug entrapment efficiency.

Acceptable range for angle of repose is between 20° and 40°. All the formulations showed an angle of repose within a range as shown in Table 1. Formulation F3, F6 and F9 showed angle of repose of 27° 40', 24° 20' and 25° 40',

respectively, which indicates a good flow property.

The drug entrapment efficiency of all the formulations was in the range of 76.6 percent to 97.8 percent, as shown in Table 1. Drug entrapment efficiency of micropellets increases with increase in percentage of sodium alginate, hydroxypropylmethylcellulose, and hydroxypropylcellulose. But the amount of calcium chloride has no significant effect

on the drug entrapment efficiency.

Verapamil hydrochloride release from the micropellets was studied in acid buffer (pH 1.2) for initial 2 h and phosphate buffer (pH 7.2) for a period of 6 h. The release pattern of micropellets was slow and spread over extended periods of time. The values of co-efficient of correlation (r) were calculated and were found to be linear for first order release as compared to zero order. Cumulative % drug released was analyzed using PRISM software. The data was best fitted to Korsmeyer and Peppas's model and good regression co-efficient was observed (Table 2). The values of diffusion co-efficient ranged between $n=0.4286$ and 0.8165 . This indicates that the release of the drug occurs by diffusion following non-Fickian transport mechanism⁸. The entrapment efficiency and cumulative percent drug released study indicated, among the nine formulations F3, F6 and F9 gave a good pattern of release and were represent among three polymers selected for the further studies (fig. 1). Scanning electron microscopy (SEM) of formulation F3 indicated that the micropellets gave rough and sandy appearance (fig. 2a). Formulation F6 (fig. 2b) indicated that the micropellets are spherical in shape and exhibited bridging. Formulation F9 (fig. 2c) shown rough surface with polymer deposits. The scanning electron microphotograph of F6 indicated bridging of micropellets which accounts for the dense nature, the surface of the micropellets was quite smooth, the porosity of the coating material was very low and the particle size was bigger, which in turn account for slow release of the drug.

Particle size of the micropellets was determined by optical microscopy. The mean particle size for F3, F6 and F9 was found to be $0.366 \mu\text{m}$, $0.655 \mu\text{m}$ and $0.511 \mu\text{m}$ respectively. Formulation F6 indicates the formation of the

thick coat around the drug particles (fig.2d), which is supported by an increase in the particle size of the micropellets. Stability studies conducted at $37 \pm 1^\circ$ and $60 \pm 1^\circ$ shown that polymers used were stable and compatible with the drug and the formulations were stable.

Prolonged release preparation intended for twice a day dosage can be developed for verapamil hydrochloride for the management of angina pectoris. The micropellets indicated good entrapment efficiency and release of the drug from the micropellets was found to be following non-Fickian diffusion mechanism, which accounts for the prolonged release of verapamil hydrochloride.

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