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Research Article

FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF GASTRO RETENTIVE FLOATING MICROSPHERES OF VERAPAMIL HYDROCLORIDE

B.Venkateswara Reddy*, G. Navaneetha
Department of Industrial Pharmacy, St.Paul's College of Pharmacy, Turkayamjal (V), Hayathnagar (M), R.R.Dist, India
*Corresponding Author Email: basu.pharmacist@gmail.com

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ABSTRACT

Floating drug delivery system is one of the novel drug delivery system. Floating drug delivery system have a bulk density less than gastric fluids and thus it remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Verapamil HCL is calcium channel blocker drug with short elimination half-life 2.8-7.4 hours Floating microspheres of Verapamil HCL were prepared by Emulsion solvent evaporation method by using HPMC K4M, HPMC K15M and Ethyl cellulose as polymers. The floating microspheres were evaluated for micromeritic properties, particle size, percentage yield, *in-vitro* buoyancy, incorporation efficiency and *in-vitro* drug release. Results show that as the concentration of polymer increases it affects the particle size, percentage yield, *in-vitro* buoyancy and *in-vitro* drug release of microspheres. The micromeritic property was found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulation F5 (drug : EC 1:2) prepared with Ethyl cellulose exhibited excellent micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release 99.86% for a period of 12 hrs. The data obtained in this study thus suggest that floating microspheres of Verapamil HCL are promising for sustained drug delivery, which can reduce dosing frequency.

Keywords: Verapamil HCL, HPMC, Ethylcellulose, Floating Microspheres.

INTRODUCTION

Recent scientific and patent literature shows increased interest in academics and industrial research groups regarding the novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT), using gastroretentive drug delivery system (GRDDS) that will provide us with new and important therapeutic options. Gastroretentive system can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs[1]. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients[2,3].

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer[4]. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. The floating microspheres have been utilized to obtain prolonged and uniform release in the stomach for development of a once daily formulation. When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy[5,6].

Verapamil HCL is a calcium channel blocker that is a class IV anti-arrhythmia agent, inhibits voltage-dependent calcium channels. Specifically, its effect on L-type calcium channels in the heart causes a reduction in ionotropy and chronotropy, thus reducing heart rate and blood pressure and its half life is 2.8 to 7.4 hours[7].

The aim of present work is to develop the floating microspheres of Verapamil HCL by emulsion solvent evaporation method. Verapamil HCL whose physiochemical properties and short half-life make it suitable candidate for floating drug delivery system.

MATERIALS AND METHODS

Verapamil was obtained from SURA labs Hyderabad. Ethyl cellulose, HPMC K4 M and HPMC K15M were purchased from Merk specialiities Pvt Limited, Mumbai.

Fourier transform infrared spectroscopy (FT-IR)

In order to check the integrity (Compatibility) of drug in the formulation, FT-IR spectra of the formulations along with the drug and other excipients were obtained and compared using Shimadzu FT-IR 8400 spectrophotometer. In the present study, Potassium bromide(KBr) pellet method was employed. The samples were thoroughly blended with dry powdered potassium bromide crystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectra was recorded.The FTIR spectra of the formulations were compared with the FT-IR spectra of the pure drug and the polymers.

Method of preparation

Emulsion solvent evaporation[8-10]

The floating microspheres of verapamil HCL were prepared by

emulsion solvent evaporation method using different polymers as follows:

The drug and polymer (HPMC K4M, Ethyl cellulose, HPMC K15M) in different proportions are weighed as per the requirements given in the table-1. The polymer was co dissolved into previously cooled mixture of ethanol: dichloromethane at room temperature. The mixture was stir vigorously to form uniform drug polymer dispersion. The above organic phase was slowly added to 100 ml distilled water containing 0.1% tween 80 by maintain the temperature at 15 – 20°C and emulsified by stirring at 500 rpm for 30 min. microspheres formed were filtered, washed with water and sieved between 50 and 30 mesh size, and dried overnight for 40°Cand then air-dried.

CHARACTERIZATION OF MICROSPHERES

Percentage Yield

The percentage of production yield was calculated from the weight of dried microspheres recovered from each batch and the sum of initial weight if starting materials. The percentage yield was calculated using the following formula

$$\%Yield = \frac{\text{Practical mass (microspheres)}}{\text{Theoretical mass (polymer + Drug)}} \times 100$$

Drug entrapment efficiency

Microspheres equivalent to 100 mg of the drug Verapamil HCL were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres. The powder was transferred to a 100 ml volumetric flask and dissolved in 10ml of methanol and the volume was made up using simulated gastric fluid pH 1.2. After 24 hours the solution was filtered through Whatmann filter paper and the absorbance was measured after suitable dilution spectrophotometrically at 235 nm[11]. The amount of drug entrapped in the microspheres was calculated by the following formula

$$\%\text{Drug Entrapment Efficiency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100$$

Micromeritic properties

The microspheres were characterized by their micromeritic properties such as particle size, bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose[12].

Bulk density

In this method floating microspheres are transferred to a measuring cylinder and is tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microspheres.

$$\text{Bulk Density} = \frac{\text{Mass of microspheres}}{\text{Bulk Volume}}$$

Tapped density

In this method floating microspheres were transferred to a measuring cylinder & tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density floating microspheres.

Percent Compressibility index was determined by using the formula,

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio of microspheres was determined by comparing tapped density to bulk density using the equation

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk Density}}$$

Angle of repose

Angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method4. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed microspheres were allowed to pass through the funnel freely on to the surface. The height and radius of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} h / r$$

where, θ - Angle of repose, h - Height of microspheres above the flat surface, r - Radius of the circle formed by the microspheres head.

Particle size analysis

Samples of the microparticles were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1unit of eyepiece micrometer was equal to 10 µm. Nearly about 100 Microparticles sizes were calculated under 45 x magnifications. The average particle size was determined by using the Edmondson's equation.

$$D_{mean} = \frac{nd}{n}$$

Where , n – Number of microspheres observed, d – Mean size range

In-vitro Buoyancy

Floating microspheres (equivalent to 100 mg) were dispersed in 900ml of 0.1 N hydrochloric acid solution (pH 1.2) to simulate gastric fluid at 37°. The mixture was stirred with a paddle at 75 rpm and after 12 hr, the layer of buoyant microspheres (W_f) was pipetted and separated by filtration simultaneously sinking microsphere (W_s) was also separated. Both microspheres type were dried at 40°C overnight. Each weight was measured and buoyancy was determined by the weight ratio of the floating microspheres to the sum of floating and sinking microsphere[13].

$$\text{Buoyancy}\% = \frac{W_f}{W_f + W_s} \times 100$$

Where W_f and W_s were the weights of the floating and settled microspheres, respectively. All the determinations were made in triplicate.

In-vitro drug release study

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5°C, 75 rpm) using the USP type – I rotating basket method in simulated gastric fluid pH 1.2 (900ml). A quantity of accurately weighed microspheres equivalent to 100 mg Verapamil HCL each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 235 nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed

simulated gastric fluid pH 1.2 maintaining sink conditions throughout the experiment[14].

Release kinetics

To study the release kinetics, data obtained from *in-vitro* drug release study was tested with the Zero order equation, First order equation, Higuchi square root law and Korsmeyer–Peppas equation[15].
Zero order equation assumes that the cumulative amount of drug release is directly related to time. The equation may be as follows:

$$C=k_0t$$

Where, k_0 is the zero order rate constant expressed in unit concentration/time and t is the time in hour. A graph of concentration vs time would yield a straight line with a slope equal to k_0 and intercept the origin of the axes.

The release behaviour of first order equation is expressed as log cumulative percentage of drug remaining vs time. The equation may be as follows.

$$\text{Log } C = \text{Log } C_0 - kt/2.303$$

Where, C = amount of drug undissolved at t time, C_0 = Drug concentration at t =0,
k = Corresponding release rate constant.

The Higuchi release model describes the cumulative percentage of drug release vs square root of time. The equation may be as follows

$$Q = K\sqrt{t}$$

Where, Q = the amount of drug dissolved at time t. K is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmeyer *et al* developed a simple, semi-empirical model relating exponentially the drug release to the elapsed time. The equation may be as follows:

$$Q/Q_0 = Ktn$$

Where, Q/Q 0 = The fraction of drug released at time t, k = Constant comprising the structural geometric characteristics, n = The diffusion exponent that depends on the release mechanism.

If $n \leq 0.5$, the release mechanism follows a Fickian diffusion, and if $0.5 < n < 1$, the release follows non-Fickian diffusion or anomalous transport. The drug release follows zero order and case II transport if n=1. But when n>1, then the release mechanism is super case II transport. This model is used in the polymeric dosage form when the release mechanism is unknown or more than one release phenomenon is present in the preparation.

RESULTS AND DISCUSSION

Compatibility studies by FTIR

The FTIR spectra of pure drug and drug along with excipients have been obtained. There was no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug and the polymers used. The data was shown in Figure 1-5.

Micrometric properties

The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing HPMC K4M as copolymer had a size range of 387.32±2.54µm to 479.52±3.25 µm. Microspheres containing ethylcellulose as copolymer exhibited a size range between 389.5±3.88 µm to 480.5±2.25 µm and microspheres containing HPMC K 15M as copolymer had a size range of 476.9±2.36 µm to489.2±3.43 µm. the particle size date is represented in the table-2. The results of other micrometric properties reveal that the prepared microspheres have good flow properties and are represented in table-2.

Yield of floating microspheres

The percentage of yield of floating microsphere formulations was in the range of 77.84±0.64% to 93.78±0.55%.At low concentration of HPMC, part of polymer solution aggregated in a fibrous structure, as it solidified prior to forming droplets or the transient droplets were broken before solidification was complete due to poor mechanical strength resulting into low yield. The results are given in the table-3.

***In-vitro* Buoyancy**

The purpose of preparing floating microspheres was to extend the gastric residence time of a drug. The buoyancy test was carried out to investigate the floatability of the prepared microspheres. The *in-vitro* buoyancy time for the formulations was more than 12 hours in the simulated gastric fluid.

Incorporation efficiency (%)

The incorporation efficiency of all the formulations was found to be in the range of 77.43±2.72% to 98.11±2.59%. Among all the formulations, formulation F5 has shown maximum entrapment efficiency which demonstrated that increase in ethylcellulose concentration causes increase in entrapment of the drug. The entrapment efficiency was good in all the formulations and is mentioned in the table-3.

***In-Vitro* drug release**

The results of *in-vitro* drug release have been represented in the table-4. The formulations F1, F2 and F3 containing HPMC K4M as polymer showed a maximum release of 99.83% after 10hours, 95.34% after 11 hours and 92.14% after 12 hours respectively.
The formulations F4,F5 and F6 containing ethyl cellulose as polymer showed a maximum release of 96.34% after 11 hours, 98.65% after 12 hours and 85.48% after 12 hours respectively.
The formulations F7, F8 and F9 containing HPMC K 15M as polyer showed a maximum release of 90.91% , 88.65% and 84.32% after 12 hours respectively.

This shows that more drug release was observed with the increase in percentage of polymers. As the polymer to drug ratio was increased the extant of drug release decreased. A significant decrease in the rate and extant of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The release of the drug has been controlled by swelling mechanism. Additionally, the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release.

From various formulations developed formulation F5 is considered to be the best with desired drug release for 12 hours and maximum incorporation efficiency when compared to other formulations.

Release kinetics

Various release kinetic models have been explored to understand the mechanism of drug release form the developed formulations. The best fit model for various formulations has been represented in the table-5. The mechanism of drug release from the optimized formulation is by peppas model and the drug release followed a combination of diffusion and erosion mechanisms.

Table 1: Formulation composition for floating Microspheres

Formulation code	Drug : polymer	Drug : polymer ratio	Dichloromethane: ethanol ratio
F1	Verapamil: HPMC K4M	1:1	1:1
F2	Drug: HPMC K4M	1:2	1:1
F3	Drug: HPMC K4M	1:3	1:1
F4	Drug: ethylcellulose	1:1	1:1
F5	Drug: ethylcellulose	1:2	1:1
F6	Drug: ethylcellulose	1:3	1:1
F7	Drug : HPMC K100M	1:1	1:1
F8	Drug : HPMC K100M	1:2	1:1
F9	Drug : HPMC K100M	1:3	1:1

Table 2: Micrometric properties of the prepared floating microspheres

Formulation code	Mean particle size µm	Bulk density(gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index	Angle of repose θ
F1	387.32±2.54	0.32±0.010	0.39±0.018	1.21±0.04	11.13±0.11	28.49±1.71
F2	452.9±2.52	0.35±0.012	0.40±0.015	1.14±0.05	12.5±0.64	27.72±1.89
F3	479.52±3.25	0.40±0.007	0.47±0.014	1.17±0.03	14.8±0.24	30.88±2.78
F4	389.5±3.88	0.36±0.014	0.44±0.014	1.22±0.01	18.18±0.33	27.00±1.93
F5	456.84±2.27	0.41±0.015	0.47±0.015	1.14±0.02	12.76±0.26	26.02±1.80
F6	480.5±2.25	0.40±0.012	0.48±0.021	1.2±0.01	16.66±0.33	26.56±1.43
F7	476.9±2.36	0.39±0.018	0.45±0.022	1.15±0.03	13.33±1.5	26.80±1.68
F8	485.82±2.3	0.41±0.015	0.48±0.027	1.17±0.01	14.5±0.86	27.11±1.59
F9	489.24±3.43	0.44±0.017	0.50±0.015	1.13±0.02	12±1.5	26.56±1.68

All the values are represented as mean ± standard deviation (n=3)

Table 3: Percentage yield and Incorporation efficiency of the prepared formulations

Formulation code	% yield	Incorporation efficiency (%)
F1	77.84±0.64	77.43±2.72
F2	82.59±0.69	87.34±2.84
F3	86.5±0.51	91.94±2.17
F4	89.67±0.66	87.11±3.01
F5	80.26±0.43	98.11±2.59
F6	88.4±0.72	92.30±2.88
F7	88.63±0.65	79.76±1.58
F8	92.29±0.74	83.91±2.02
F9	93.78±0.55	90.38±2.34

Table 4: In-vitro release data for various floating microsphere formulations of verapamil

Time(hr)	Cumulative % Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	5.72	5.12	4.83	8.43	5.34	4.23	4.07	2.18	1.34
2	12.83	11.23	10.23	15.32	12.31	9.56	12.32	8.56	6.32
3	23.18	21.24	18.65	24.21	20.38	16.43	21.44	16.48	11.52
4	30.28	28.45	25.42	33.62	28.45	22.71	30.23	23.74	20.71
5	41.28	36.45	31.32	40.12	37.20	31.78	38.86	32.18	28.64
6	53.29	43.28	40.44	48.46	44.38	38.92	43.29	41.28	35.43
7	63.64	55.72	50.54	55.38	52.27	48.64	51.65	48.65	41.45
8	79.01	62.15	58.63	65.15	61.46	56.38	60.46	56.43	50.54
9	88.63	76.34	65.43	73.26	70.34	62.81	69.45	64.87	58.42
10	99.83	84.36	74.32	84.12	78.43	70.30	78.34	70.34	67.54
11	99.83	95.34	82.14	96.34	89.25	78.64	85.34	79.65	75.43
12	99.83	95.34	92.14	96.43	98.65	85.48	90.91	88.65	84.32

Table 5: Release kinetic profile for the formulations

F. code	Zero-order		First-order		Higuchi		Korsmeyer Peppas		Best fit model
	Slope	R^2	Slope	R^2	Slope	R^2	Slope(n)	R^2	
F1	10.0788	0.9866	-0.0103	0.8735	42.1702	0.9459	1.2373	0.9981	Peppas
F2	8.3828	0.9897	-0.0080	0.9262	34.9151	0.9553	1.2194	0.9974	Peppas
F3	7.5105	0.9915	-0.0071	0.9649	31.2952	0.9589	1.2065	0.9974	Peppas
F4	8.0848	0.9987	-0.0079	0.9661	32.7994	0.9784	1.0136	0.9982	Zero-order
F5	7.8970	0.9973	-0.0075	0.9654	32.7606	0.9730	1.1941	0.9989	Peppas
F6	7.2970	0.9926	-0.0069	0.9723	30.5593	0.9629	1.2640	0.9983	Peppas
F7	7.8061	0.9963	-0.0073	0.9736	32.4207	0.9827	1.2614	0.9883	Peppas
F8	7.5515	0.9924	-0.0069	0.9739	32.0077	0.9720	1.5307	0.9831	Zero-order
F9	6.8121	0.9861	-0.0064	0.9746	29.1972	0.9658	1.7867	0.9751	Zero-order

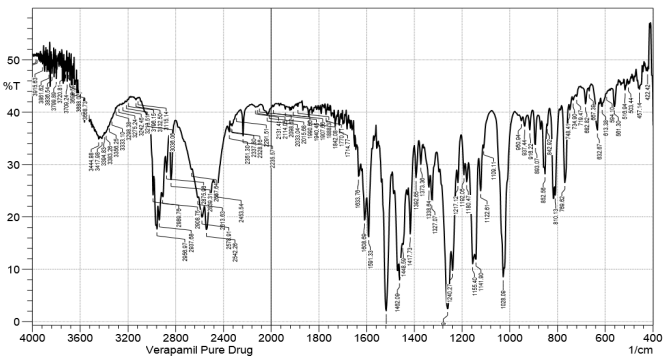

Figure 1: FTIR spectra of pure drug

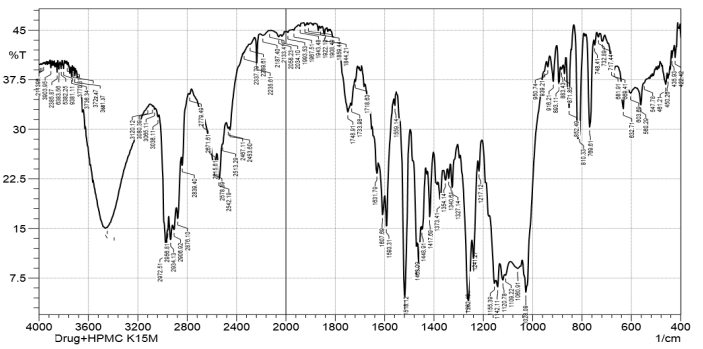

Figure 2: FTIR spectra of Drug + HPMC K15M

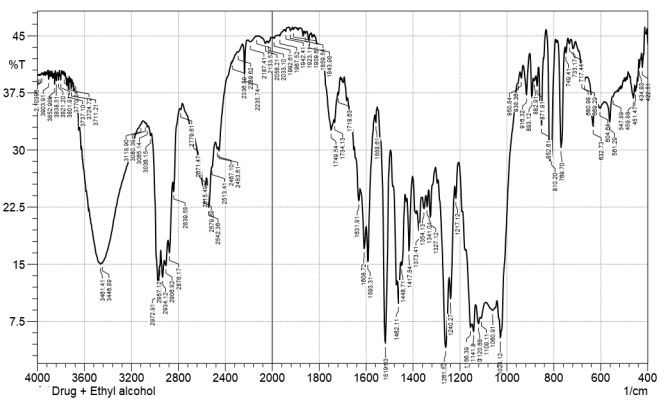

Figure 3: FTIR spectra of Drug+ Ethyl alcohol

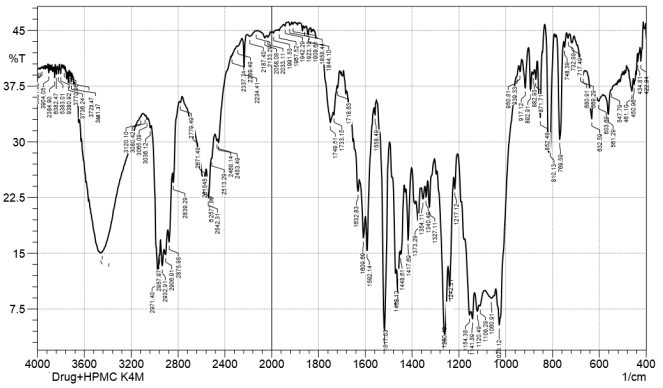

Figure 4: FTIR spectra of drug+ HPMC K4M

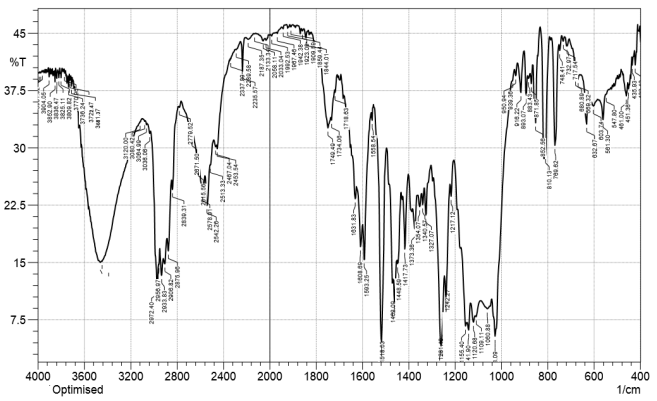

Figure 5: FTIR spectra of optimized formulation

CONCLUSION

Floating microspheres of Verapamil HCL were successfully prepared by using HPMC and Ethyl cellulose as polymers by emulsion solvent evaporation. The flow properties of all the prepared microspheres were good as indicated by low angle of repose and low compressibility index. The good flow properties suggested that the microspheres produced were nonaggregated. The mean particle size of microspheres was in the range of 102.33-420.53 µm depending upon the type of polymer used. The particle size increased significantly as the amount of polymer increased. The percent yield of all floating microspheres formulation was more than 60% suggesting that the methods used for encapsulation was effective. The percent yield was significantly increased as the amount of polymer was increased in each preparation method. The entrapment efficiency was good in all the cases. This suggested that optimized parameters were used in the method of preparations. The *in-vitro* buoyancy was more than 70% after 12 hours indicated satisfactory performance of proposed formulations. The percent buoyancy increased significantly as the amount of polymer was increased in each preparation method. *In-vitro* release of floating microspheres ofVerapamil HCL was found to be in following order. F5>F3>F7>F8>F6> F9>F4>F2>F1. Among all formulations, F5 was found to be the best formulation as it release Verapamil HCL 98.65 % in a controlled manner with constant fashion over extended period of time (up to 12 hrs). In vitro release data fitted into various kinetic models suggest that the release obeyed mixed order kinetic, Zero order mechanism and non fickian control (anomalous diffusion) with swelling.

Hence, finally it was concluded that the prepared floating microspheres of Verapamil HCL may prove to be potential candidate for safe and effective controlled drug delivery over an extended period of time which can reduce dosing frequency.

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