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Devlopment and Characterization of Diltiazem Hydrochloride Microspheres

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ABSTRACT

Diltiazem hydrochloride is calcium channel blocker used in the treatment of hypertension. The present work aims towards the study of effect of combination of natural polymer on percent release of drug and effect of concentration of cross linking agent on microsphere rigididization time. In the present work for sustaining action of drug, microspheres of Diltiazem Hydrochloride were prepared by orifice ionic gelation technique using HPMC and Xantan gum and their combination as a polymer with various ratios. The prepared microcapsules were free flowing, non sticy and evaluated for various parameters like drug content, percent drug release, shape & size and polymer drug reactions. All the formulations were shown satisfactory results. The obtained results stated that the natural polymer can be used for sustaining the release of drug.

Keywords: Diltiazem Hydrochloride , HPMC, Xantan Orifice Ionic Gelation Technique, Microspheres.

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INTRODUCTION

The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature which hold several advantages. Microspheres can encapsulate many types of drugs including small molecules, proteins, nucleic acids and are easily administered through a syringe needle. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time. (Benita S. et.al 2005) Diltiazem hydrochloride, a calcium channel blocker, is widely used for the treatment of angina pectoris, hypertension and arrhythmias. It is administered orally (tablets, capsules, sustained release tablets /capsules) and parenterally (intravenous). The usual dose of diltiazem is 180-240 mg/day. The conventional tablet and capsule is administered 3 or 4 times a day due to its short biological half-life of about 6 h. The problems of frequent administration and variable low bioavailability (40-60%) after oral administration of conventional tablet or capsules have been attenuated by designing diltiazem in the form of sustained release tablet or capsule. Gupta.et.al (2010) and Jain et.al (2001). The sustained release forms are administered two times a day due to its limited residence time in the gastrointestinal tract. The microcapsules of diltiazem would prolong the residence time and thereby improve and enhance the bioavailability Peh et.al(2002) and Lencki et.al. (1989). The previous studies reported the mucoadhesive drug delivery systems of diltiazem inthe form of tablets for oral route and transdermal patches; however, there is no report on microcapsules. Therefore, the objective of the present study was the development and evaluation of gastroretentive microspheres containing diltiazem hydrochloride using various polymers for prolonged gastrointestinal absorption Gohel et.al (2005) and Vyas et.al.(2004). An attempt was also made to develop microspheres with high entrapment efficiency. The objective of the present work was to develop, characterize (pre- and post-formulation parameters) and evaluate aceclofenac mucoadhesive microcapsules by following orifice-ionic gelation technique using sodium alginate (SA) as the release rate retarding polymer with Xanthan Gum, hydroxypropyl methyl cellulose (HPMC polymers and are economic and easily available synthetic hydrophilic polymers.

EXPERIMENTAL DETAILS

Diltiazem Hydrochloride is obtained as gift sample from Themis laboratories,Ltd. Mumbai.

Sodium Alginate and Calcium Chloride is procured from Thomas Baker, Mumbai, Xanthan gum and HPMC is obtained from Colorcon Asia Pvt. Ltd., Goa.

Formulation of Sustained Release Microsphere Procedure

Microspheres containing diltiazem hydrochloride were prepared by orifice ionic gelation technique using combination with HPMC and Xantam gum as a polymer. The homogeneous solution of polymer and sodium alginate was prepared in 25 ml distilled water and the drug is added and stirred to form viscous mixture, which was then extruded through a syringe of 18 gauge needle into calcium chloride solution. these droplet were retained in calcium chloride

solution for 15 min to complete the curing reaction and to produce rigid spherical microsphere. microspheres collected by decantation and the product thus separated was washed with purified water to remove the traces of calcium and then dried at 40^0C. Carvalho et.al (2010) Mankala et.al (2005) Santhosh Kumar Mankala et.al (2011) and .Radha et.al (2012) .

Table No. 1: Formulation Chart

Formulation Batch	Core: Coat	Coat Composition		
		Sodium alginate	HPMC	Xanthan gum
FA	1:3	2	1	0
FB	1:4	2	2	0
FC	1:5	2	3	0
FD	1:3	2	0	1
FE	1:4	2	0	2
FF	1:5	2	0	3
FG	1:6	2	1	3
FH	1:6	2	2	2
FI	1:6	2	3	1

Evaluation of Diltiazem HCl Microsphere

Particle Size Determination

Particle size was determined by using an optical microscope under regular polarized light, and the mean particle size was calculated by measuring 50-100 particles with the help of a calibrated ocular micrometer.(Martin et.al (2001). Mazzo David. et.al (2010)

Bulk Density

It is determined by using graduated cylinder, the accurately weighed quantity of microcapsules added to cylinder and tapped three times. The volume noted, and bulk density is calculated using formula

$$\text{Formula:} \quad \rho_b = \frac{M}{V}$$

Where, m = mass of sample, v = volume of sample, ρ_b=Density

Gattani et.al (2008) and Chaudhari et.al (2005)

Tapped Density

It is determined by using graduated cylinder, the accurately weighed quantity of microcapsules added to cylinder and tapped hundred times. The volume noted, and bulk density is calculated using formula

$$D_o = M / Vp$$

Where,
D_o = bulk density, M = weight of samples in grams, Vp = final tapped volumes of microsphere in cm^3**v. (**Das M.K. et.al 2005 and Kristmundsdottir T. et.al 1996**)**

Angle of Repose

It was carried out using funnel, at sufficient height funnel was fixed and, microcapsules were added through it until the pile touches to the tip of funnel. Height and radius of pile measured and angle of repose calculated using formula.

$$\tan\theta = h\backslash r$$

where, h = height and r = is radius of pile
Chaudhary et.al (2005)

Percentage Yield

The percentage yield of the prepared microsphere determined by weighing after drying. The measured weight of prepared microspheres was divided by the total amount of all the non–volatile components used for the preparation of the microspheres, which gave the total percentage yield of microspheres.

$$\text{Yield} = \frac{\text{actual wt of product}}{Totalweigh tofexceipe nts} X\,100$$ Ashok Kumar et.al (2011**)**

Drug Entrapment Efficiency

About 100mg of microsphere is weighed accurately and crushed in glass mortar. Powdered microspheres were suspended in 50 ml of phosphate buffer pH 7.4. After 24 hr the solution was filtered and filtrate was analysed for drug content at 222.5 nm. The results of % Diltiazem Hcl loading and encapsulation efficiency were calculated using Equation
It is calculated by using percent drug content.

Formula $$\frac{\text{Estimated \% Drug content}}{\text{Theorotical \% Drug content}} X\,100$$

In-vitro **Release Study of Microspheres**

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In vitro drug release studies were carried out using USP 25 (Type II) apparatus in 900ml of dissolution medium (n=3) maintained at 37±1^{0}C at a speed of 100 rpm. in phosphate buffer P^H 7.4 was used as dissolution medium. Aliquots of 10ml were withdrawn at predetermined time intervals using calibrated pipette during a 12 hours period and filtered. An equivalent amount of fresh dissolution medium, maintained at 37±1^{0}C was added after withdrawing each sample to maintain the sink conditions. The drug concentrations in the sample analyzed spectrophotometrically (double beam UV, Thermo) at 237nm. The mean of three readings was used to determine concentration. Das et.al (2008**)** and Pandey et.al (2011)

Scanning Electron Microscopy (SEM)

The surface topography of the optimized microsphere examined under a FEI-Philips XL-30 Analytical Electron microscope (Diya labs,Mumbai). The sample was loaded on copper sample holder and sputter coated with platinum. Pandey et.al (2011)

RESULTS

Table No.2

Batch	% yield	% Drug Entrapment	Avg particle size	Bulk Density (g/cm^3)	Tap Density (g/cm^3)	Angle of Repose (θ)
FA	84.14±0.9	82.92±1.4	291.46±8.3	0.298	0.522	25^0-15′
FB	86.40±3.6	85.12±2.4	323.44±6.9	0.542	0.654	26^0 -20′
FC	90.25±1.9	86.30±1.1	356.88±8.6	0.526	0.636	25^0-12′
FD	82.62±2.6	86.48±2.6	263.84±8.3	0.430	0.508	30^0-20′
FE	82.71±1.4	85.94±1.5	327.65±7.5	0.482	0.528	25^0-06′
FF	83.50±1.7	86.46±2.6	356.22±8.1	0.516	0.616	31^0-24′
FG	84.60±3.2	88.56±3.1	406.69±6.9	0.452	0.572	30^0-12′
FH	94.25±1.5	92.30±3.4	426.40±7.3	0.468	0.506	27^0-24′
FI	96.47±3.1	87.02±1.1	432.62±9.4	0.534	0.622	30^0-20′

Table No.3 In vitro drug release profile

Time (min)	Cumulative Percent Drug Released								
	Formulation Code								
	FA	**FB**	**FC**	**FD**	**FE**	**FF**	**FG**	**FH**	**FI**
0	0	0	0	0	0	0	0	0	0
1	18.44	24.62	20.94	16.07	20.57	18.89	14.69	20.96	17.85
2	23.89	29.92	25.71	20.87	26.89	24.29	19.18	27.47	23.68
3	27.22	34.59	30.34	26.56	31.72	28.76	23.93	33.63	28.26
4	35.37	42.35	37.24	32.37	37.45	35.12	35.76	42.72	37.14

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5	41.36	49.58	43.61	38.58	42.37	40.47	47.73	54.19	49.13
6	47.15	56.61	50.41	42.67	49.72	45.67	54.76	61.15	56.68
7	55.06	61.89	59.45	51.92	56.64	54.42	67.34	73.81	68.52
8	63.17	68.75	66.56	63.18	67.53	65.37	74.56	82.72	76.12
9	72.82	78.26	77.27	75.25	79.83	77.07	83.07	88.63	81.42
10	79.32	87.56	85.06	78.74	85.02	83.27	86.27	90.94	88.34
11	85.24	92.85	89.78	83.67	89.51	86.71	88.63	94.49	90.49
12	91.64	94.74	93.29	86.95	93.17	90.62	93.49	97.78	95.85

Fig.No.1-In vitro drug release studies of formulation FA to FC

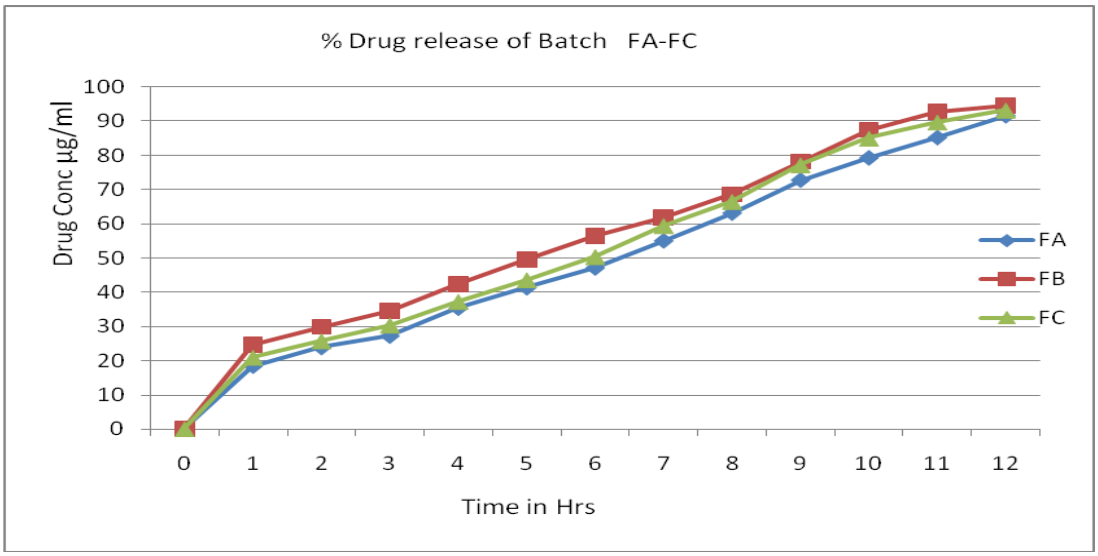

Fig No.2-In vitro release studies of formulation FD to FF

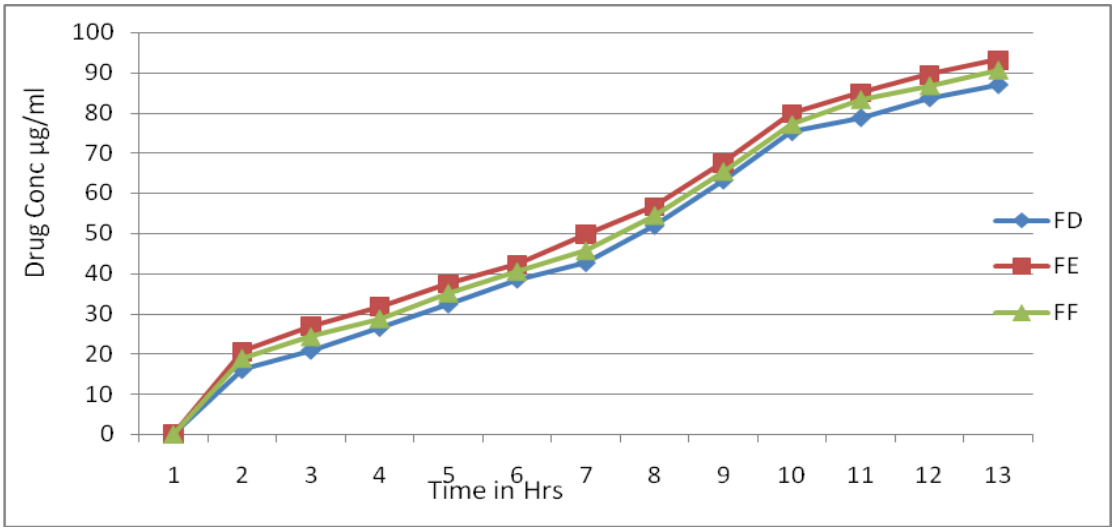

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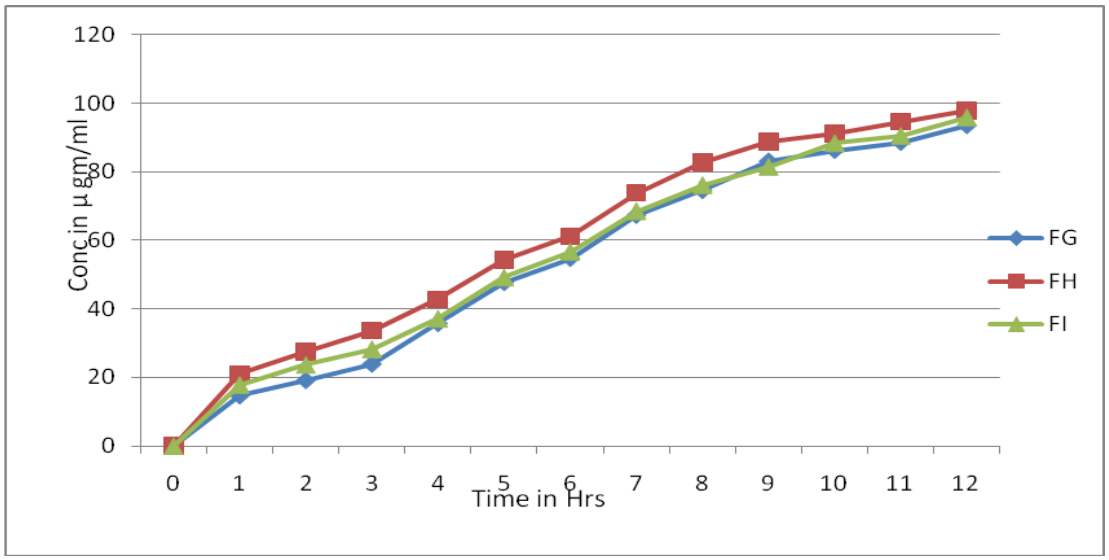
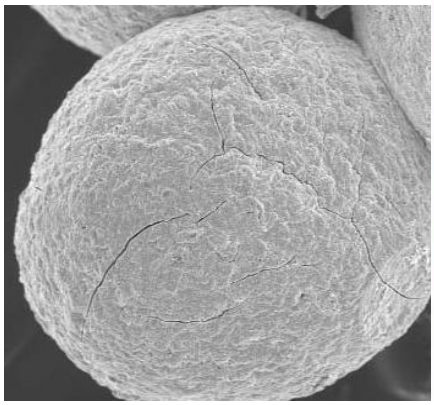
Fig .No.3 In vitro release studies of formulation FG to FI





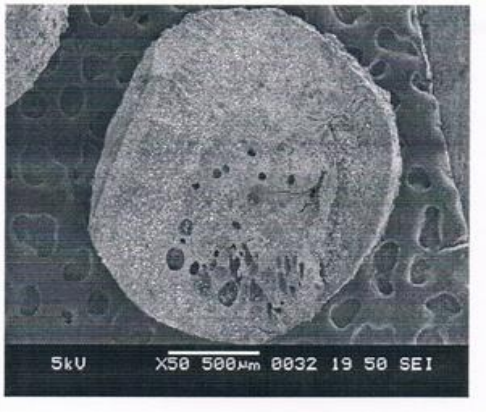


Fig No 4: size range at at X50

Fig No 5: cross section view at X50

RESULT AND DISCUSSION

The prepared microsphere gives good percentage yield to be 96.47 % among all the batches. It was found that average percentage yield of microsphere was greater than 82% for all. The percent drug entrapment of diltiazem Hcl in all formulation of combination of HPMC and Xanthan gum polymer was found to be good i.e. above 84 %. The microsphere of batch FH formulation showed an entrapment of 92.30 %. All the formulations were subjected to in-vitro dissolution studies. The results revealed that formulations with the drug–polymer ratio 1.0:1.0 (FA, FD and FG) showed drug release rates in the range of 91.-94% when compared (FD, FE and FH) which showed a drug release rates from 90. -93% to and those of (FG, FH and I) which have displayed drug release rates in the range of 93.-97% to 86.95 to over a period of 12 hours. This indicates that as the polymer concentration increased, the drug release rate was found to be retarded. The synergistic effect was observed when the HPMC was combined with xanthan

gum, burst effect was also observed by other investigators who suggested the addition of the hydrocolloids such as HPMC in relatively large amounts. Hence batch FH indicates the better results than batch I. The hydration rate of hypromellose polymer relates to its hydroxypropyl substitutes percentage. The HPMC contains the higher amount of these groups and produce strongly viscose gel that plays an important role in drug release especially at the beginning of the release profile. Therefore, the quick hydration and subsequent gel formation is a foremost and important property of an excipients for it to be used in sustained-release formulations. As formulation FH shown 97.78% cumulative drug release pattern, which was according to the Acceptance Table of Test 2 given in USP-NF 2007 for the 12 hours dosing of diltiazem hydrochloride. When the HPMC combined with the natural gums is used for controlling the drug release, the process of drug release from matrix involves solvent penetration in to the matrix, gelatinization of the polymer, dissolution of the drug and diffusion of the drug through resultant layer. Concomitantly, the outer layer becomes fully hydrated and dissolves, this process is generally referred to as erosion. The smooth surface of microspheres as seen by SEM might be due to complete homogeneity of drug and polymer. The outer surface of the microspheres was smooth and dense, while the internal surface was porous. The shell of the microspheres also showed some porous structure. It may be caused by the evaporation of the solvent entrapped within the shell of microspheres after forming a smooth and dense skin layer. The surface topography revealed a spherical surface for all the formulations and a round cavity enclosed by an outer shell composed of the drug and polymer.

CONCLUSION

In the above view of findings it can be suggested that HPMC when combined with the hydrophilic natural gums shows the synergistic effects and hence can be utilized to prolong the release of Diltiazem HCl. The overall frequency of administration of a drug candidate like Diltiazem HCl was successfully reduced to 2 times a day, which generally requires dosing in 3 to 4 times a day in conventional tablet dosage form.The improved patient convenience might thus be obtained by the administration of such a dosage form with minimal blood level fluctuations. The release retardant materials are cheap, readily available, safe, having wide regulatory acceptance and easy to handle for economic point of view. It may beneficial to adopt such simple technology for the commercial production of sustained release microsphere.

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