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Design and Characterization of Diltiazem Hcl Microspheres by Using Ethyl Cellulose and Poly Vinyl Pyrolidine as Polymer

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ABSTRACT

The present study is aimed towards Design and characterization of gastro retentive floating multiparticulate oral drug delivery system of Diltiazem hydrochloride, which can provide sustained release delivery of the drug. In the present study, preparation of Diltiazem HCl Microspheres was formulated using Ethyl cellulose and PVP K-90 as the rate controlling polymer, with an aim to prolong its release. six formulations of Diltiazem hydrochloride were prepared as gastro retentive floating microspheres by solvent evaporation technique using polymers such as ethyl cellulose, polyvinyl pyrolidine K-90 and in different ratios. The prepared floating microspheres were evaluated for different physicochemical tests such as, Particle size analysis, drug encapsulation efficiency, SEM, Invitro release studies was performed. The results of all the physicochemical tests of all formulations were found to be satisfactory. The mean particle size of prepared microspheres increased but the drug release rate from the microspheres decreased as the polymer concentration increased. The *in vitro* drug release was found to be in the range of 56.22% to 98.93 % at the end of 6 hours. It is concluded that these floating microspheres can be selected for the development of gastro retentive drug delivery system of Diltiazem hydrochloride for potential therapeutic uses.

Keywords: Gastro Retentive Microspheres, Diltiazem hydrochloride, Ethyl Cellulose, Polyvinyl Pyrolidine K-90.

INTRODUCTION

A gastro retentive dosage form (GRDF) releases medications in a controlled manner for extending the absorption phase of drugs which show a limited and narrow absorption window at the upper part of the gastrointestinal tract or drugs intended to treat local ailments in the gastro duodenum. This mode of administration may prolong the time period in which the blood drug concentrations are within the "therapeutic levels" and improve therapy. Besides being locally active in the stomach, these extended-release dosage forms with prolonged residence time in the stomach are also highly desirable for drugs that are unstable in the intestinal or colonic environment, and/or have low solubility at higher pH values [1]. Therefore, development of GRDFs has been a major pharmaceutical challenge during the past few decades.

The gastro retentive dosage forms (GRDFs) has been designed in large part based on the following approaches [2]: (a) low density form of the DF that causes buoyancy above gastric fluid; (b) high density DF that is retained in the bottom of the stomach; (c) bioadhesion to the stomach mucosa; (d) slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients; (e) expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter.

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluid and therefore remain floating in the stomach without affecting gastric emptying rate for prolonged period. The drug is slowly released at the desired rate from the floating system. After release of drug, the residual system is expelled from the stomach. These floating dosage forms may have a number of advantages in oral drug delivery because they prolong retention in the gastrointestinal tract, particularly in the stomach. Gastro retentive delivery system facilitates sustained drug release and maintains high concentrations of drug within the gastric mucosa. This property may also be performed for treatment of *Helicobacter pylori* infection. [3].

Diltiazem HCl, a benzodiazepine, voltage sensitive ca $^{2+}$channel blocker with a high therapeutic potential but with a very short biological half life was encapsulated within microsphere.

Diltiazem is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). The antihypertensive, antianginal and antiarrhythmic effects of Diltiazem is believed to be related to its specific cellular action of selectively inhibiting transmembrane influx of calcium in cardiac muscle, coronary arteries, and systemic arteries and in cells of the intra cardiac conduction system. [4] Given orally, 90–100% of Diltiazem is absorbed, but due to high first pass metabolism, bioavailability is much lower (40–60%), half life is 4-5 hours (with chronic dosages) and not cleared by hemodialysis [5]. Diltiazem hydrochloride are easily absorbed from gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from blood circulation [6], therefore, it was proposed to develop a gastro retentive floating drug delivery system to enhance the absorption of the drug intended to increase the bioavailability of the drug.

MATERIALS AND METHODS

1. Materials:

Diltiazem Hcl was received as a gift from M/s Microlabs, Bangalore, India. Ethyl cellulose (EC), polyvinyl pyrolidine K-90 (PVP K-90 were procured from NICE Chemicals, Mumbai.

All other reagents and solvents used were of pharmaceutical or analytical grade.

2. Methods:

2.1 Preparation of Diltiazem Hcl microspheres: [7-9]

Floating microspheres containing Diltiazem hydrochloride were prepared by an emulsification solvent evaporation technique [6] using ECand PVP K-90 polymers (Table 1,2).Accurately weighed Ethyl cellulose and PVP K-90 in Different ratio 1:1, 1:2 were dissolved in 25ml of acetone to form a homogenous polymer solution. Core material, Diltiazem HCl was

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added to the polymer solution and mixed thoroughly. This organic phase was slowly poured at 30ºC into liquid paraffin (100 ml) containing 1% w/w of span-80 with stirring at 900 rpm to form a smooth emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth walled, rigid and discrete microspheres were formed. The microspheres were collected by decantation and the product was washed with petroleum ether (40-60ºC), three times and dried at room temperature for 3 hrs. The microspheres were then stored in a desiccator over fused calcium chloride.

Table No. 1: Formulations of Diltiazem hydrochloride Microspheres prepared with different Polymers and Polymer mixtures (Drug: Polymer =1:1)

Contents of Formulations	FM1	FM2	FM3
Diltiazem hydrochloride (gm)	2	2	2
Ethyl cellulose(gm)	2	-	1
PVP K-90 (gm)	-	2	1
Acetone (ml)	25	25	25
Span 80 (ml)	0.5	0.5	0.5
Liquid paraffin (ml)	100	100	100

Table No. 2: Formulations of Diltiazem hydrochloride Microspheres prepared with different Polymers and Polymer mixtures (Drug: Polymer =1:2)

Contents of Formulations	FM1	FM2	FM3
Diltiazem hydrochloride (gm)	2	2	2
Ethyl cellulose (gm)	4	-	2
PVP K-90 (gm)	-	4	2
Acetone (ml)	50	50	50
Span 80 (ml)	1	1	1
Liquid paraffin (ml)	200	200	200

3. Evaluation Of Flurbiprofen Microcapsules:

3.1. Percentage yield: [10]

The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microcapsule.

% yield = (Actual weight of product / Total weight of excipient and drug) x 100

3.2.Incorporationefficiency: [11]

In 100ml volumetric flask 25mg of crushed microcapsules were taken and dissolved with small quantity of ethanol of the volume is made up to mark with pH 6.8 and stirred for 12 hours. After stirring the solution was filtered through whatman filter paper and from the filtrate appropriate dilutions were made and absorbance was measured at 237 nm by using UV-spectrophotometer 1700 (Shimadzu).

3.3. Micromeritic properties: [12-14]

Particle size: Determination of average particle size of the Diltiazem HCl microspheres was carried out by the optical microscopy method. A minute quantity of microcapsules was spread on clean glass slide and average sizes of 100 microcapsules were determined in each batch.The floating microspheres are characterized by their micromeritic properties such as bulk density, and angle of repose.

Angle of Repose: Determination of angle of repose Diltiaem HCl microspheres were carried out by employing fixed funnel method.

$$\text{Angle of repose } \theta = \tan^{-1} (H/R)$$

H = Height of the pile , R = Radius of the pile

3.4. Scanning electron microscopy: [15]

The samples for SEM analysis were prepared by following method. Dry microcapsules brass stub an coated with gold in an ion sputter. Then picture of microcapsules were taken by random scanning of the stub. The SEM analysis or the microcapsules was carried out by using Lieca stereomicroscope EZ4D and Magnified 10x20 xs.

3.5. Drug release: [16]

In vitro release studies: *In vitro* dissolution profile of each formulation was determined by employing USP XXIII rotating basket method (900 ml of pH 6.8-phosphate buffer, 100 rpm, 37±0.5 ◦C). Microspheres equivalent to 120 mg of Diltiazem HCl was loaded into the basket of the dissolution apparatus. Five milliliters of the sample was withdrawn from the dissolution media at suitable time intervals and the same amount was replaced with fresh buffer. The absorbance of the filtrate was determined at wavelength of 237 nm by using UV–VIS spectrophotometer, against pH 6.8 as blank.

RESULT AND DISCUSSION

Results are shown in Table 3,4 (Fig 1,2) Diltiazem hydrochloride loaded microspheres having a fairly high yield (78.51 – 94.14%) were obtained. The entrapment efficiencies ranged from 85.21 – 90.8%. The incorporation efficiency of formulations, FM1 – FM3 was more than formulations FM4 – FM6. The highest incorporation efficiency of formulation having drug: polymer ratio 1:1 can be explained through the fact that the amount of polymer in per unit drug is lesser than that in other formulations.

Table No. 3: % Yield of microcapsules

S. No.	Formulation code	Percentage Yield (%)
1	FM 1	94.14
2	FM 2	91.53
3	FM3	89.47
4	FM4	78.51
5	FM5	79.32
6	FM6	81.13

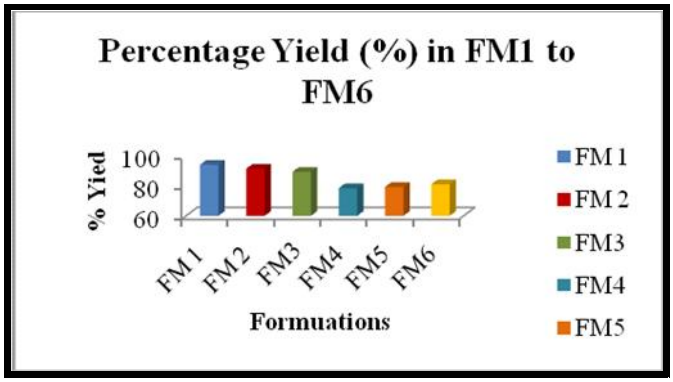

Fig. 1: % yield of microspheres

Table No. 4: Incorporation efficiency

S.no	Formulation code	Entrapment Efficiencies (%)* ± S.D.
1	FM 1	95.73
2	FM 2	92.28
3	FM3	90.8
4	FM4	85.21
5	FM5	87.84
6	FM6	88.12

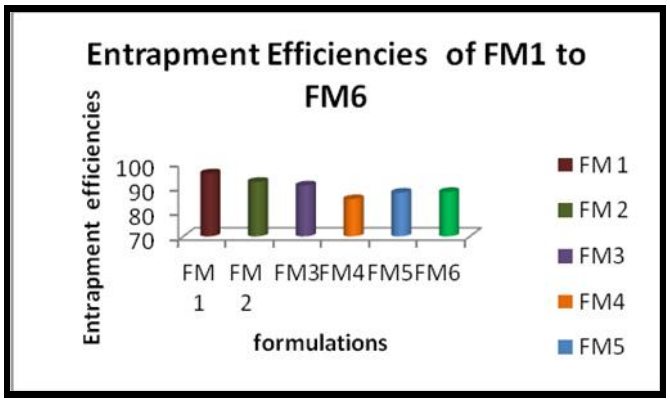

Fig. 2: Incorporation efficiency

The arithmetic mean particle size of the formulations was determined by the optical microscope fitted with an ocular micrometer and stage micrometer. The average mean particle sizes of the microcapsules were found to be 221.76±0.451, 236.22±2.134, 262.34±2.732, 322.48±2.801, 349.32±4.101, 372.64±4.234 (as shown in table 5.) For formulations FM1, FM2, FM3, FM4,FM5 and FM6 respectively. The mean particle size of the microcapsules significantly increased with increase in polymer concentration due to high viscosity of medium at a higher polymer concentration resulting in enhanced interfacial tension and diminished shearing efficiency. The angle of repose of microcapsule ranges from 21° 82" ± 0.20, 22° 86" ± 0.62, 23° 30" ± 0.55 and 25°55" ± 0.40, 27.29 ±0.38, 28.32 ±0.45 (as shown in table 5). The values of angles of repose indicate excellent flow properties.

Table No. 5: Micromeritic properties of Microspheres

Batch code	Average Particle size in µm	Bulk Density (gm/ml)	Angle of repose(θ)
FM 1	221.76±0.451	0.794±0.004	21.82±0.20
FM 2	236.22±2.134	0.785±0.003	22.86 ±0.62
FM3	262.34±2.732	0.803±0.012	23.30 ±0.55
FM4	332.48±2.801	0.810±0.021	25.55 ±0.40
FM5	349.32±4.101	0.771±0.008	27.29 ±0.38
FM6	372.64±4.234	0.802±0.002	28.32 ±0.45

Table No. 6 : Particle size Range of Microspheres

Particle size Range (µM)	FM1	FM2	FM3	FM4	FM5	FM6
200-250	53	60	15	9	10	5
250-300	15	12	62	11	18	17
300-350	10	8	18	27	60	25
350-400	5	3	5	15	23	53

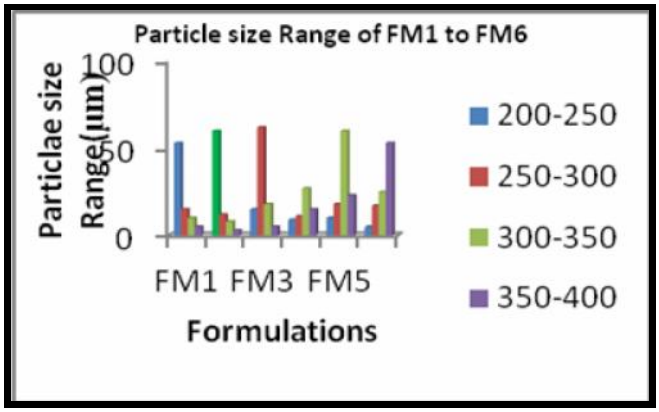

Fig. 3: Particle size Range of Microspheres

Morphology of microcapsules was examined by scanning electron microscopy. The view of the microcapsules showed smooth surface morphology exhibited range of sizes within each batch. The outer surface of microcapsules was smooth and dense, while the internal surface was porous. The shell of microcapsules also showed some porous structure it may be caused by evaporation of solvent entrapped within the shell of microcapsules after forming smooth and dense layer.

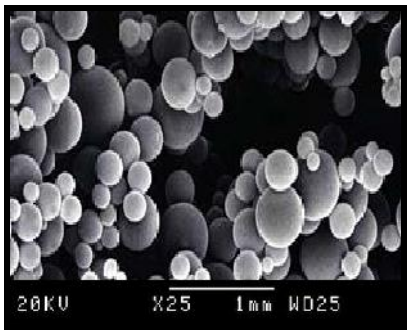

Fig 4 FM1

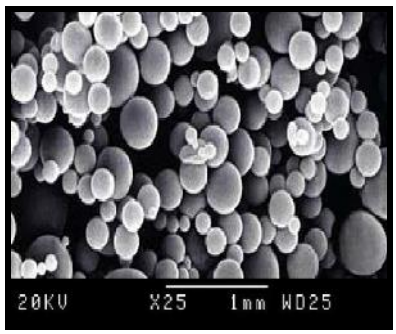

Fig 5 FM2

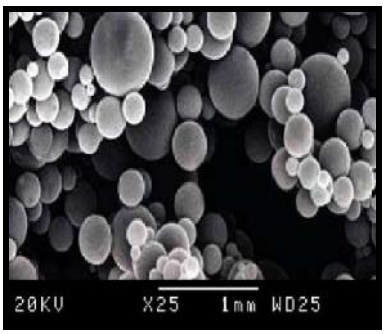

Fig 6 FM3

Invitro Drug release:

In vitro release studies were carried out using USP XXIII dissolution assembly. The release profile obtained for all the four formulations were shown in Fig. 7. It was observed that the drug release from the formulations decreased with increase in the amount of polymer added in each formulation. The release of drug from polymer matrix takes place after complete swelling of the polymer and as the amount of polymer in the formulation increase the time required to swell also increase thereby decrease in the drug release. However, the release showed a bi-phasic release with an initial burst effect. In the first 60 min drug release was 40.36%, 20.02%, 22.43% and 24.27%,14.6%,13.36% for FM1, FM2, FM3,FM4, FM5 and FM6 respectively. The mechanism for the burst release can be attributed to the drug loaded on the microcapsule or imperfect entrapment of drug. The overall cumulative % release for FM1, FM2, FM3 ,FM4,FM5 and FM6 were found to be 98.93%, 78.56%, 89.6%, 74.34%,56.22% and 65.23% at the end of 12th hour.

Table No. 7: Invitro Dissolution study

S. NO.	Time (hrs)	Formulation FM1 (DTZ: EC, 1:1)	Formulation FM2 (DTZ : PVP K-90 1:1)	Formulation FM3 (DTZ:E-RL100: EC: PVP K-90 1:0.5:0.5)	Formulation FM4 (DTZ:EC 1:2)	Formulation FM5 (DTZ:PVP K-901:2)	Formulation FM6 (DTZ: EC:PVP K-90 1:1:1)
1	0	0	0	0	0	0	0
2	1	40.3	20.02	22.43	24.27	14.6	13.36
3	2	58	30.05	37.93	33.68	20.97	19.39
4	3	72.24	37.06	51	38.67	24.72	24.89
5	4	79.15	40.09	60.96	47.34	27.71	28.34
6	5	83.56	44.15	69.14	53.21	31.91	32.58
7	6	86.8	48.21	75.35	57.23	36.77	36.81
8	7	90.11	51.9	79.74	62.76	41.12	40.92
9	8	95.48	59.43	81.9	67	45.24	45.06
10	9	97.2	63.23	82.7	68.91	48.24	49.23
11	10	97.9	68.7	85.5	70.65	50.72	55.09
12	11	98.2	74	87.2	72.41	53.9	60.48
13	12	98.93	78.56	89.6	74.34	56.22	65.23

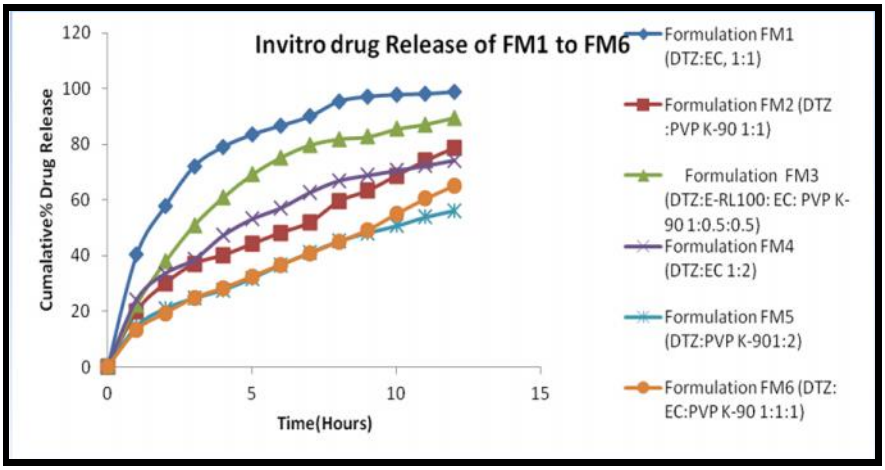

Fig. 7: Invitro Drug Release of FM1 to FM6

CONCLUSION

Microcapsules may prove to be potential candidate for safe and effective sustained drug delivery. From the results it seems that formulation FM1 was found to be satisfactory in terms of excellent Micromeritic properties, yield of microcapsule, (94.14%), incorporation efficiency (95.73%) and highest in vitro drug release of 98.93% in a sustained manner with constant fashion over extended period of time for 12 hrs. It was observed that concentration of polymers affect all the evaluation parameter significantly. It is concluded that these floating microspheres can be selected for the development of gastro retentive drug delivery system of Diltiazem hydrochloride for potential therapeutic uses.

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