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Review Article

DEVELOPMENT AND EVALUATION OF MODIFIED RELEASE DOSAGE FORMS BASED ON GASTRO RETENTIVE AND OSMOTIC TECHNOLOGY PRINCIPLES

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ABSTRACT

The present study involves the design and characterization of floating microspheres with Dilteazem Hydrochloride as model drug for prolongation of tonic clonic jerk time, microsphere of Dilteazem Hydrochloride, was developed to reduce the frequency of drug administration, ease of dose adjustment and improve patient compliance. In this study, the shape and surface morphology of microspheres were characterized by scanning electron microscopy. *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of polymer concentration, solvent composition, particle size, drug entrapment efficiency and drug release were also studied. The synthesized microspheres exhibited prolonged drug release (> 10 h) and remained buoyant for > 24 h. The drug entrapment efficiency was in the range 50-70 %. At higher polymer concentration, the average particle size was increased and the drug release rate decreased. In vitro studies revealed diffusion-controlled drug release from the microspheres. Among all the formulations (F1-F6), F3 is the optimized formulation of Dilteazem Hydrochloride was prepared by solvent evaporation techniques using Ethyl cellulose as polymer and particle size, microsphere efficiencies and in vitro release of the fabricated microsphere were evaluated. Particle sizes of the microspheres were influenced by the concentration of Ethyl cellulose and stirring speed. From the results of the in vitro study shows that the desired release rate is achieved by ethyl cellulose. The object of this study was to develop and evaluate stable microspheres of Dilteazem Hydrochloride drug an antiepileptic drug using combination of Eudragit and ethyl cellulose as polymer which delivers the drug at a controlled rate for a prolonged period of time. Ethyl cellulose used in this study and it is showing hard binding of microspheres.

Keywords: Dilteazem Hydrochloride, Sustained release, Ethyl Cellulose.

INTRODUCTION

Micro sphere small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm (1 mm)). Micro spheres are sometimes referred to as micro particles. Micro spheres can be manufactured from various natural and synthetic materials. Glass micro spheres, polymer micro spheres and ceramic micro spheres are commercially available. Solid and hollow micro spheres vary widely in density and, therefore, are used for different applications. Hollow micro spheres are typically used as additives to lower the density of a material. Solid micro spheres have numerous applications depending on what material they are constructed of and what size they are. [1-4] Polyethylene and polystyrene micro spheres are two most common types of polymer micro spheres. Micro spheres vary widely in quality, sphericity, uniformity, and particle size distribution. The appropriate micro sphere needs to be chosen for each unique application. Micro spheres are discrete spherical particles ranging in average particle size from1 to 50 microns. [5-6] Because of their size and shape; Micro spheres offer a ball-bearing effect which will impart finished products with an elegant silky texture, increased payoff, and enhanced slip. Micro spheres are also able to scatter light to diminish the look of fine lines on the skin, while letting enough light through so the look of the skin

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is natural. [7-8] A special use of Micro spheres is in mascaras. The non-absorbent grades of silica's of different diameters have a volatizing effect, with minimum absorbency. [9-10]

MATERIAL AND METHODS

Dilteazem Hydrochloride generous gift from Alna biotech India, ethylcelloulose (ethoxy content 48%) and cellulose acetate, Span80, acetone, conc. HCl, potassium hydrogen liquid paraffin, n- hexane, phosphate, were purchased from NS scientific centre, India. All other reagents were of analytical grade.

Equipments

Shimadzu (Model No. 8410S), Electronic melting point apparatus (Stuart TM.) SMP 10, BibbyScietific (limited stone Staffordshire, ST15, India), KNAUER HPLC system (India), Erweka® dissolution apparatus, Mechanical Stirrer (India), Titerteck® ultrasonic cleaner, Labtech® Scan lab. water bath, vacuum, Scan Lab® sensitive balance (Germany), FTIR Spectroscopy, and pH meter, Hanna instruments (Japan).

Preparation of Microspheres

Microspheres were prepared by the solvent evaporation technique as employed by Struebel *et al.* 2008. [11-13] EC were dissolved in a mixture of ethanol and dichloromethane at room temperature (Table I). Different Dilteazem Hydrochloride microspheres were prepared using different drug:polymer ratios (which maintaining a constant amount of drug), different temperatures, organic dispersed phase type and polymer types. This was poured into 300 mL water containing 0.01% Tween 80 maintained at a temperature of 20–40 °C and subsequently stirred at ranging agitation speed for 10 min to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with water and dried in vacuum. [14-15]

In vitro drug release

A USP basket apparatus has been used to study *in vitro* drug release from microspheres (18–20). In the present study, drug release was studied using a modified USP XXIV (17) dissolution apparatus type I (basket mesh : 120, equals 125 _m) at 100 rpm in distilled water and 0.1 mol L–1 HCl (pH 1.4) as dissolution fluids (900 mL) maintained at 37 ± 0.5 °C. Withdrawn samples (10 mL) were analyzed spectrophotometrically as stated above. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition. All experiments were performed in triplicate linear regression was used to analyze the *in vitro* release mechanism. [16-17]

Statistical Analysis

Experimental results were expressed as mean SD. Student's t-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Six formulations (F1, F2, F3, F4, F5 and F6) of micro sphere of ethyl cellulose -polymer ratios were formulated. The products were dried for 24 hr in a desiccator containing fused CaCl2. After drying, the % of yield was determined by weighing method and found 70.8, 65.30, 74.36, 80.0 and 85.00 % for formulation F1, F2, F3, F4 F5 and F6 respectively (Table I). Formulation F4 showed highest percentage of yield (81.0%) and F2 showed lowest percentage of yield (60.35%). Compressibility index, the packing factor of various formulations was compared with the pure drug. The higher the percentage of compressibility index, lesser the flow property among the various formulations F1 has the highest compressibility index and F3 has lowest compressibility than other formulations. In comparison to drug, the various formulations show excellent flow property. Packing factor of all the formulations was compared with pure drug. The pure drug has more packing factor as compared to other formulations. All the formulations have shown free flowing nature. Among all the formulations, F4 shows the lowest packing factor that indicates free flow property. But formulation F1 shows more packing factor as compared to other formulations which shows less free flowing property, specified in Table II.

The % of drug content varied from 46% to 70%. Formulation F4 showed highest percentage of drug content having drug: polymer ratio (1:2) and formulation F2 showed lowest % of drug contents having drug: polymer ratio (1:1.3) as shown in Table III. The drug entrapment efficiency was high in case of F4 and low in case of F3 Table III. The low encapsulation efficiency is due to low water entrapment and low solubility effect of drug in the formulation. The floating test was carried out to investigate the floatability of prepared microspheres. The ethyl cellulose coated floating microspheres have shown good floating ability (Table IV). The particle size distribution analysis was performed on all formulations using sieves of size 1 mm, 60 µm, 200 µm, 300 µm and the data were given in Table V. From this study, most of floating microspheres were collected above sieve range of 315 µm. Highest amount was retained between the range of 60 µm-355 µm. The shape and surface topography confirms spherical microspheres with nearly regular surface. Fig. 1 indicate the size range of microspheres; B and C smoothness of the surface of spherically shaped microspheres. The structure of Dilteazem Hydrochloride is confirmed by FTIR

spectroscopy. It shows a broad absorption band at 2437.02 cm^{-1} due to the stretching frequency of the –C-H group of methyl. The band at 2757.30 cm^{-1} is due to C-H stretching vibration. The band around 1448.02 cm^{-1} & 1379.83 cm^{-1} are assigned to –CH2 scissoring and –O-H bending vibration respectively. The band at 1157.0 cm^{-1} is due to >CH-O-CH_2 stretching and at 1439.67 cm^{-1} at due to strong carbonyl absorption. The band at 917.86 cm-1 is due to C-O-C symmetrical stretching. The studies revealed that there was no significant interaction between drug and polymer. The characteristic –NH_2, COOH and cyclohexane group of drug was unchanged in case of microspheres. Standard curve of 0.1N HCL shown in Graph-1.

In case of F2, with an increase in the polymer content from 50% to 100%, the release of the drug at 1 h was decreased from 80% to 74%. However, at 5 & 8 h, the bursting effect was noticed (86% and 89% respectively). Hence, in the subsequent formulation F3, the polymer content was increased from 100% to 150% of drug content and it was observed that the release of the drug at 1 h decreased to 60%, which continued up to 12 h for release of 94% without any bursting effect in between. It was found that the drug release profile follows zero order from 2 h to 10 h. Further, in formulation F4, the polymer content was increased from 140% to 200% of the drug content, which exhibited the drug release of 30% at 1 h and 65% at 12 h which continued further. The study reveals that the drug release profile obeys the first order of release kinetics from 0 to 3 h and further the drug release profile followed zero order release up to 12 h. In formulation F6, by increasing the polymer contents up to 225% of drug content, it was found that the drug release at 1 h was decreased to 21% which continued up to 10 h (80%). No release was noticed after 10 h. It was found that the complete release pattern follows zero order kinetics. The highest release was 78%. Due to low entrapment of fluid into the formulation, the drug release stopped further.

Hausner's Ratio:- A hausner ratio of<1.25 indicates a powder that is free flowing where as>1.25 indicates poor flow ability it is calculated by the following formula [18] The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material it is calculated by the formula

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

Ph=PI/PB

Where pb is the freely settle bulk density of the powder the Hausner's ratio is not an absolute property and material its value can vary depending on the methodology used to determinehausner ratio.

Scanning of Dilteazem Hydrochloride Microspheres Scanning Electron Microscopy

The surface morphology and particle size of microspheres were determined by Scanning Electron Microscopy using a JEOL JSM-T330A scanning microscope (Japan). Dry microspheres were placed on an electron microscope brass stub and coated with gold in an ion sputter.

***In vitro* Dissolution Studies**

By the use of dissolution Instrument, Paddle Type Method (Apparatus)Range of 100 Rpm And fill Up 900 Ml Of 0.1N HAL(Ph1.2) For 2 Hr and Ph 6.8 for 3 Hr And Ph 7.4 For 8 Hr At 35±0.5^{0}c At Set Time. The amount of Dilteazem Hydrochloride drug was measured spectrophotometrically At 276nm for Acidic Phase Ph7.4 At 272 And Ph 6.8 at 274. The data obtained for *in vitro* release were fitted into equations for the zero-order, first-order and Higuchi release models (24–26). The interpretation of data was based on the value of the resulting regression coefficients. The *in vitro* drug release showed the highest regression coefficient values for Higuchi's model, indicating diffusion to be the predominant mechanism of drug release. The drug dissolution rate of diffusion-controlled systems in biological fluids is affected by the variability of pH and epileptic condition. Hence, a comparison was made in order to see the effect of different dissolution media on drug release. The solubility of EC and Eudagritin distilled water and 0.1 mol L–1 HCl at 40°C was reported to be 13.4 and 210 mg mL–1, respectively Tai (2002). This lower aqueous solubility might have result in a marked decrease in drug release. Significantly lower cumulative drug release (p < 0.05) was observed in distilled water compared to that in 0.1 mol L–1 HCl. F3 formulation shows effective microspheres of Dilteazem Hydrochloride.

Table 1: Batch Specifications of the Prepared Microspheres

Batch code	Polymer ratio (EC/Eudragit® L100)	Temperature (°C)	Solvent ratio (acetone, ethanol)
F-1	1:1	20-40	1:1
F-2	1:3	20-40	1:1
F-3	1:2	20-40	1:1
F-4	1:5	20-40	1:3
F-5	1:4	20-40	2:1
F-6	1:6	20-40	3:1

Table 2: Composition of Microspheres Formulation by Stirring Speed.

Ingredients	FI	F2	F3
Liquid paraffin	50ml	50ml	50ml
Span 80	35	35	35
Dichloromethane	10	10	10
ethanol	10	10	10
Ethyl cellulose	2gm	2gm	2gm
drug	10mg	10mg	10mg
Stirring speed	800	1000	1200

Table 3: Ingredient Content of Microsphere.

Ingredients	F4	F5	F6
Liquid paraffin	50	50	50
Span 80	0.35	0.35	0.35
Dichloromethane	10	10	10
ethanol	10	10	10
Ethyl cellulose	2gm	4gm	6gm
Drug	10mg	10mg	10mg
Stirring speed	1000	1000	1000

Table 4: Formulation content

S. No.	Component	Quantity
1	Dilteazem Hydrochloride	100mg
2	10 to 15 ml	100mg
3	Dichloromethane(DCM)	10ml
4	Ethanol	10ml
5	Liquid light paraffin	50 ml
6	Span 80	0.5%
7	N hexane	10 to 15 ml

Table 5: Swelling index 0.1N HCl

Time	F1	F2	F3
1h	0.2±0.20	0.4±0.21	0.5±0.26
2h	0.4±0.22	0.7±0.36	0.8±0.33
3h	0.7±25	0.9±0.33	1±0.11
4h	0.9±29	1.1±0.41	1.2±0.28
5h	1±22	1.3±0.49	1.5±0.33
24h	1.2±33	1.4±0.56	1.6±0.42

FTIR OF DILTEAZEM HYDROCHLORIDE DRUG:

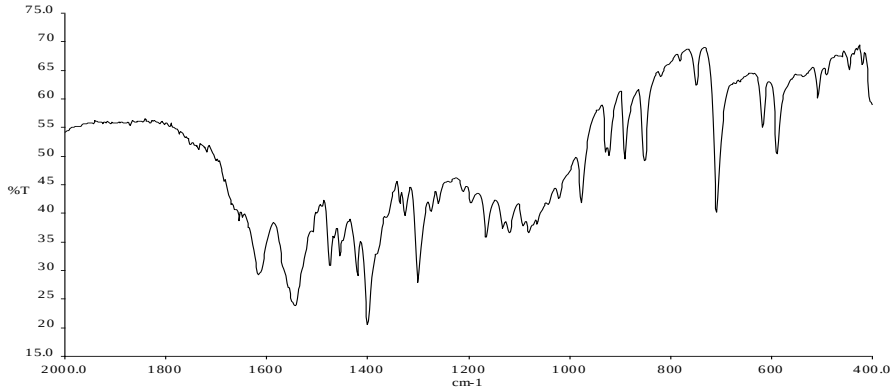


Figure 1:

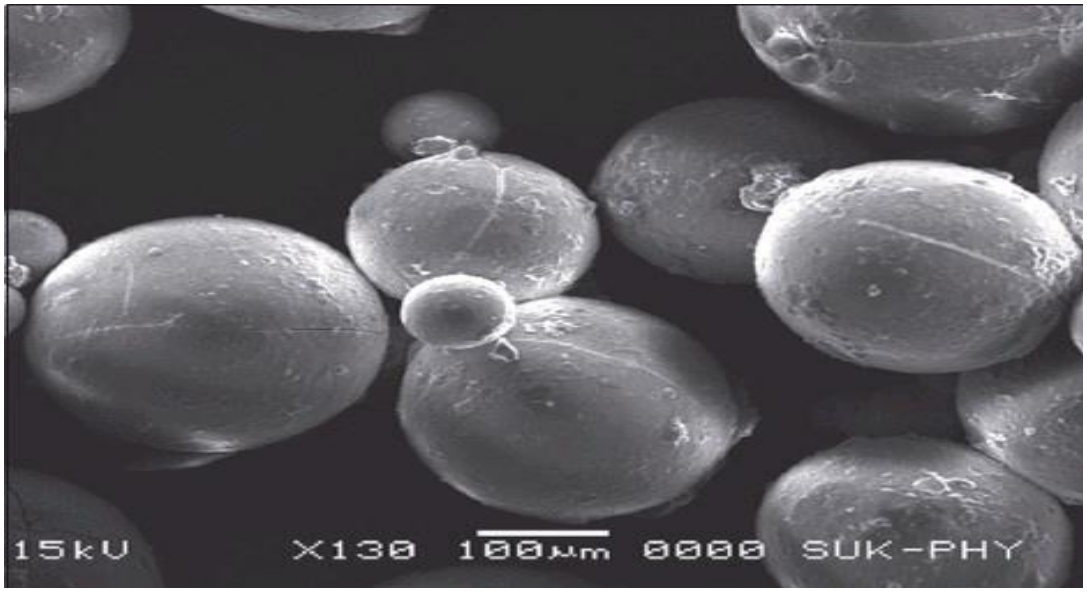
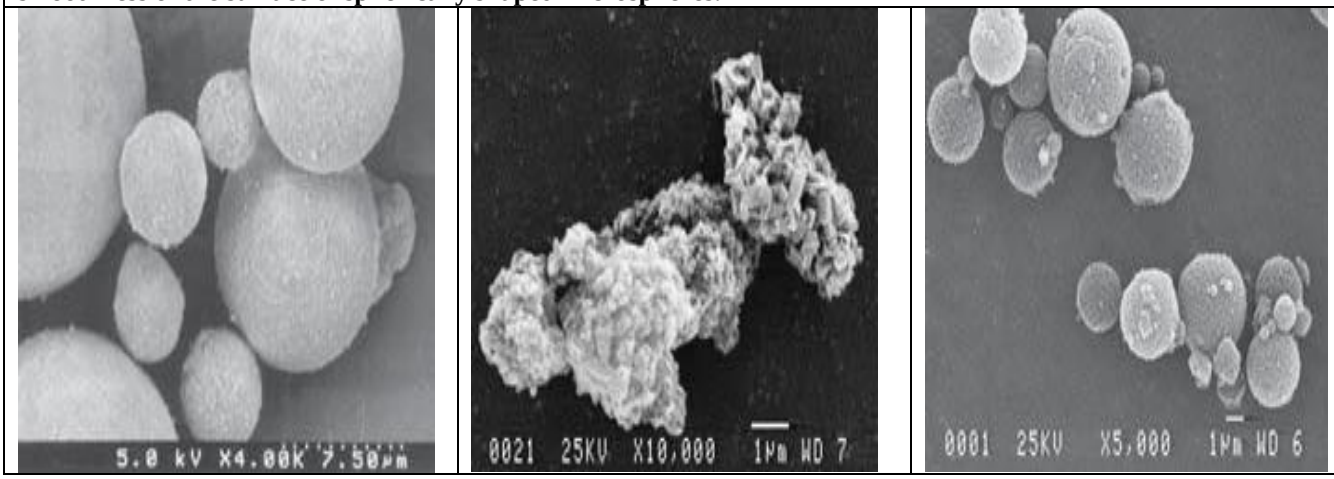


Figure 2: Scanning electron microphotographs of floating microspheres A: the sizerange of microspheres; B and C smoothness of the surface of spherically shaped microspheres.



CONCLUSION

The floating microspheres of Dilteazem Hydrochloride were prepared by solvent evaporation method with different ratios of polymer. Based upon the all obtained values, concluded that all the formulation followed the uppercase II transport diffusion. The object of this study was to develop and evaluate stable microspheres of Dilteazem Hydrochloride drug an antiepileptic drug using ethyl cellulose as polymer which delivers the drug at a controlled rate for a prolonged period of time.

The analytical method (solvent evaporation) used in this all study was found to be suitable for the estimation of Dilteazem Hydrochloride drug in different solvent/media by this process we found regressive values for making standard curve. This process found that Dilteazem Hydrochloride is freely soluble in water acetone, ethanol in the buffer ph 7.4. Ethyl cellulose used in this study and it is giving a very good hard binding of microspheres. The size of microspheres mainly affected by stirring speed as stirring speed increased the size of microspheres was decreased. The mirosphere efficiency was increased by increase of polymer concentration and decrease with increase in drug polymer ratio.

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