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Formulation and *In Vitro* Characterization of Diltiazem Hydrochloride Microballoons as a Novel Gastro-Retentive Drug Delivery System

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Abstract

A sustained release system for Diltiazem Hydrochloride designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of microballoons as gastro-retentive drug delivery system. Microballoons were prepared by the o/o emulsion solvent diffusion-evaporation method utilizing two different acrylic polymers like Drugcoat RS 100, Drugcoat RL 100 and one ethyl cellulose with three different ratios of polymers. The prepared microballoons were evaluated for polymer compatibility, percentage recovery, drug entrapment, micrometric properties, surface morphology, *in vitro* floatation ability, *in vitro* release studies, and release kinetics and stability study. Scanning electron microscopy confirmed their hollow structures for its buoyancy. All Formulations show good floatability and drug entrapment. Formulation F_6 containing drug and Drugcoat RS 100 (1:2) which showed appropriate balance between release rate and buoyancy could be advantageous in terms of increased bioavailability of Diltiazem Hydrochloride. The formulation was found to be physically and chemically stable as per ICH guidelines.

Keywords: Diltiazem hydrochloride, microballoons, drugcoat, o/o emulsion solvent diffusion-evaporation method.

Introduction

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed.

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The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine) (Rouge and Deshpande 1996).

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating system (Lee et al. 1999), high-density systems, (Hwang et al. 1996), bioadhesive systems (Akiyama et al. 1995), swellable systems (Fix et al. 1993) and other delayed gastric emptying devices have been developed.

With regard to the floating devices, Kawashima et al. (1992) developed hollow microspheres (microballoons) to prolong GRT of the dosage form and found that microballons were very useful for sustained release action (Kawashima et al. 1992), Murata et al. (2000) prepared calcium induced alginate gel beads that, upon oral administration, were capable of floating on gastric juice (Murata et al. 2000). Moreover, Lee et al. (2001) devised the preparation method of floating microspheres using acrylic resin (Lee 1999, Choi 2001). Streubel et al., 2003 developed a single unit, floating drug delivery system based on low density foam power and matrix-forming polymers (Streubel et al. 2003). Sato et al. (2004) prepared microballons of aspirin, riboflavin, indomethcin by emulsion solvent diffusion method utilizing enteric acrylic polymers (Sato et al. 2004).

Diltiazem hydrochloride (DTZ) is a calcium channel blocker belonging to the benzothiazepine family. It is indicated for the treatment of hypertension and management of chronic stable angina. DTZ undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A which results in less than 4% of its oral dose being excreted unchanged in urine. Bioavailability of DTZ is ~30% to 40% owing to an important first pass metabolism. It has an elimination half-life of 3.5 hours and has an absorption zone from the upper intestinal tract (Indian Pharmacopoeia 1996, Martindale 2007).Efficacy of the administered dose may get diminished due to incomplete drug release from the device above the absorption zone (Iannuccelli et al. 1998). DTZ requires multiple daily drug dosage in order to maintain adequate plasma concentrations. Therefore, it is a suitable model candidate for gastroretentive formulation. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. High solubility of DTZ was a major challenge in designing its controlled drug delivery system.

The objective of the present study was to develop microspheres with Microballoons (MB) of Diltiazem HCl in order to achieve an extended retention in the upper GIT and avoiding dose dumping which is major limitation of conventional dosage form like tablets. MB prepared using different acrylic polymer with different permeability characteristics, which may result in enhanced absorption and thereby improved bioavailability, better therapeutic efficacy and improved patient compliance.

Materials and Methods

Materials

Diltiazem Hydrochloride (Cipla Ltd., Mumbai) was employed as a model drug. Drugcoat RS 100 and Drugcoat RL 100 (Vikram Thermo (India) Ltd., Ahmedabad), Ethyl Cellulose (S.D. Fine Chemicals Ltd., Mumbai) were used as rate controlling polymer. Light liquid Paraffin (Burgoyne chemicals, New Delhi) was used as dispersing agent.

Methods

Preparation of Microballoons

Microballoons were prepared by o/o emulsion solvent diffusion-evaporation Method to create the hollow inner core. Firstly, Polymer like Ethyl cellulose, Drugcoat RS 100 and Drugcoat RL 100 and Diltiazem HCl as a drug(0.3g) was mixed in an organic solvent like acetone (8ml) in a different ratio (1:1, 1:1.5, 1:2) using blending solvent i.e. Isopropanol (5ml). The solution or slurry containing the drug and polymer was introduced in to 200ml of light liquid paraffin. After that organic solvent is evaporated by continuous stirring using mechanical stirrer (Remi, Mumbai) with 1200 rpm speed for about 2 hours. Finely developed microballoons were then filtered, washed with petroleum ether 40-60^{0}c until free from oil. Finally, The Collected microballoons were dried 3-4 hours at 40^{0}c in oven. The solvent removal leads to polymer precipitation at the interface of droplets, forming cavity and thus making them hollow to impart the floating properties (Yu-meng Wei 2008, Raymond 2009). (See Table 1)

Table 1.Formulation composition of floating microballoons of DTZ

Formulation Code	DTZ HCl	EC	DC- RS 100	DC-RL 100
F1	1	1	-	-
F2	1	1.5	-	-
F3	1	2	-	-
F4	1	-	1	-
F5	1	-	1.5	-
F6	1	-	2	-
F7	1	-	-	1
F8	1	-	-	1.5
F9	1	-	-	2

DTZ HCl- Diltiazem Hydrochloride, EC- Ethyl Cellulose, DC-RS 100- Drugcoat RS 100 and DC-RL 100- Drugcoat RL 100

Compatibility Studies

Fourier transforms infrared spectroscopy (FTIR) spectra of the pure Diltiazem HCl drug and the polymer blends with pure drug were produced by using KBr. Both were triturated in mortar using pestle and subjected to FTIR with a Shimadzu 00722 PC FTIR. Background spectrum was collected before running each sample. The samples were analyzed between wave numbers 4000 and 400 cm^{-1} (Subrahmanyam 2004).

Morphological Study using SEM

The microballoons of selected batch F6 were subjected for scanning electron microscopy (SEM) study. The surface topography of the microballoons of selected batch was examined under a JEOL- 6380A Analytical Electron microscope (VNIT, Nagpur). A small amount of powder was spread on an aluminum stub, which was placed after gold sputtering in SEM chamber (JSM 6390® USA) Photographs were taken.

Micromeritic studies

The microballoons are characterized by their micromeritic properties such as particle size, tapped density, Carr's index and flow property (Aulton 1998, Martin 1991).

Recovery

Recovery or percentage yield of microballoons containing a drug was determined by the weight ratio of the dried microballoons to the loading amount of drug, polymers and other non- volatile components (Rout et al. 2009).

Floating Behavior

Fifty milligrams of the floating microballoons were placed in 100 ml of the simulated gastric fluid (0.1 N HCL - pH 1.2) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer (Remi, Mumbai). After 12 hours, the layer of buoyant microspheres was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microballoons were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles (Jain 2006, Patil 2009).Percentage buoyancy is very much important to predict the floating behavior of microballoons in the GI tract for sustained release of drug.

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

Where, W_f and W_s are the weight of the floating and settled microparticles.

Incorporation efficiency

For incorporation efficiency, accurately weighed about 50 mg of dried microballoons were taken and busted mechanically to get powder, dissolved in 0.1 N HCl by ultrasonication at room temperature and kept it aside for 12 h. Filtered through filter paper and then amount of drug present was estimated by using UV spectrophotometer (Shimadzu, Japan) at a λ_{max} of 237nm (Patil 2009, Yang 2004). The amount of drug incorporation in the microspheres was calculated by using the following formula;

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

In-Vitro Release Studies

The release rate from floating microspheres was determined using USP XXIII (Electrolab, eight station model) basket type dissolution apparatus. An accurately weighed amount of floating microspheres equivalent to dose of drug 300 mg was filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution test apparatus. 900 ml of the 0.1 N HCl containing 0.02% w/v of Tween 20 was used as the dissolution medium. Tween 20 added to dissolution medium, counteracted the downward pulling at the liquid surface by lowering surface tension, because the relatively high surface tension of simulated gastric fluid causes the highest decrease of surface area at the air fluid interface. The dissolution fluid was maintained at 37 ± 0.5°C with a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 1 ml of samples were withdrawn after every each 60 min interval up to 12 h and replaced by fresh dissolution media maintained at 37 ± 0.5°C, withdrawn sample was filtered through a 0.25 μm membrane filter (Millipore) and diluted with same dissolution media if necessary, and finally analyzed by using UV spectrophotometer to at a λ_{max} of 237 nm. (Patil 2009, Jain 2009).

Model fitting

The model fitting for % cumulative release was done using PCP Disso v2.08 software to find the best fits kinetic equation for the dissolution profile (Costa et al. 2001).

Stability studies: Stability studies were carried out at 40±2^{0}c and 75± 5% relative humidity for one month (Dumpeti Janardan 2008, Ramkanth 2010).

Result and Discussion

The microballoons of Diltiazem HCl were successfully prepared by using O/O emulsion solvent diffusion-evaporation method. Different batches of various ratios of drug and polymer like Ethyl Cellulose (10 CPS), Drugcoat RS 100 and Drugcoat RL 100 combination were successfully prepared along with constant speed and temperature.

Good solubility of the polymer in the solvent was a prerequisite for the preparation of microspheres. The combination that yielded the best microballoons with good morphology was taken up for further studies. The selected formulation were loaded with the drug and evaluated on the basis of its percentage recovery, buoyancy, entrapment efficiency, release studies, surface morphology and Drug interaction studies.

Drug-Interaction Study

From the FT-IR spectra of the Diltiazem HCl and the combination spectra of drug and excipients, it was observed that all the characteristic peaks of Diltiazem HCl i.e., peaks for N-H stretch, C=O stretch (acetate) and C=O stretch (lactam) were present in the Diltiazem HCl as well as in combination spectra. Therefore we don't found any major changes in peaks of above mentioned important functional groups indicating the compatibility of the drug with the polymers (see Figure 1).

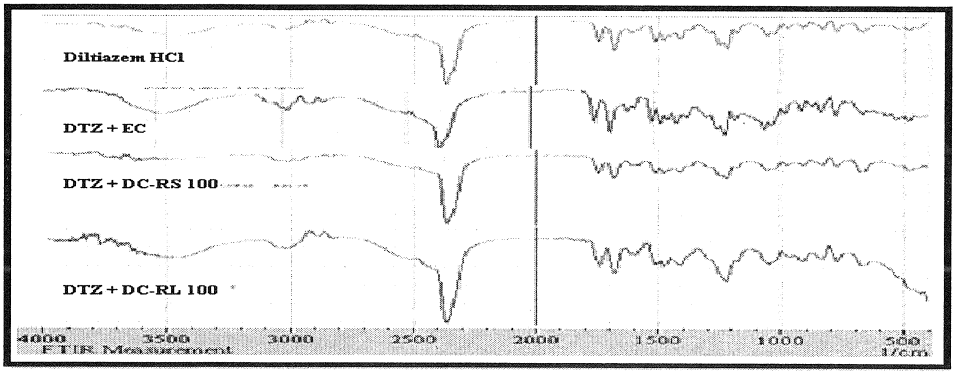


Figure 1. Drug-interaction study

Micromeritic Studies of Microballoons

The various batches have the average particle size in the range of 249μm to 398μm. The particle size was increased as the viscosity of solution was increased i.e. as the polymer concentration is increased. The tapped density value ranged from 0.31-0.55, bulk density in between 0.29-0.50, Carr's index in between 8.3-19.35% and Hausner's ratio within 1.06-1.21.

This significant difference in the densities may be caused by the presence of low density polymer in the microsphere. All formulation showed excellent flowability as expressed in terms of angle of repose was found within the range of 28^0 to 36^0, which is an appreciable limit for microspheres to show flow property while formulating in the dosage form (See Table 2).

Table 2. Micromeritic studies

Batches	Average particle size (mm)	Tapped density (g/cm3)	Bulk density (g/cm3)	% Comp.Index	Hausner's ratio	Angle of repose (q)
F1	356.42±4.87	0.31±0.001	0.29±.001	8.3	1.06	31°26'
F2	381.93±10.2	0.34±0.003	0.28±.002	17.39	1.2	30° 64'
F3	398.73±6.98	0.40±0.004	0.36±.005	9.09	1.1	36° 86'
F4	249.68±7.16	0.50±0.02	0.43±.004	13.33	1.16	36° 46'
F5	262.38±2.48	0.55±0.001	0.50±.002	9.52	1.1	35° 13'
F6	281.26±4.54	0.47±0.002	0.40±.001	15	1.17	28° 81'
F7	223.21±4.73	0.45±0.004	0.37±.03	17.24	1.21	33° 17'
F8	267.12±3.17	0.52±0.005	0.44±.002	14.28	1.18	32° 46'
F9	291.63±9.52	0.54±0.004	0.45±.006	19.35	1.2	29° 74'

Percentage recovery

The prepared microballoons give good percentage recovery. The percentage yield of microballoons was determined by weighing after drying for some time in oven. The percentage recovery was found in between the range of 54.21 to 89.95 %. The maximum percentage yield was found of F7 batch and was noted to be 89.95 % among all the batches (See Table 3).

Table 3. Parameters of microballoons

Formulations	% Recovery	% Entrapment	% Buoyancy
F1	83.26 ± 0.21	80.16 ± 0.21	43.94 ± 0.12
F2	86.15 ± 0.18	74.29 ± 0.56	51.06 ± 0.66
F3	88.98 ± 0.08	52.18 ± 0.75	44.07 ± 0.25
F4	54.21 ± 0.10	51.61 ± 0.56	58.36 ± 0.40
F5	70.00 ± 0.07	76.40 ± 0.39	52.90 ± 0.33
F6	88.70 ± 0.20	83.97 ± 0.57	78.66 ± 0.50
F7	89.95 ± 0.03	77.62 ± 0.59	71.28 ± 0.89
F8	69.29 ± 0.09	43.13 ± 0.45	65.87 ± 0.62
F9	79.09 ± 0.11	69.79 ± 0.26	69.06 ± 0.24

Drug entrapment

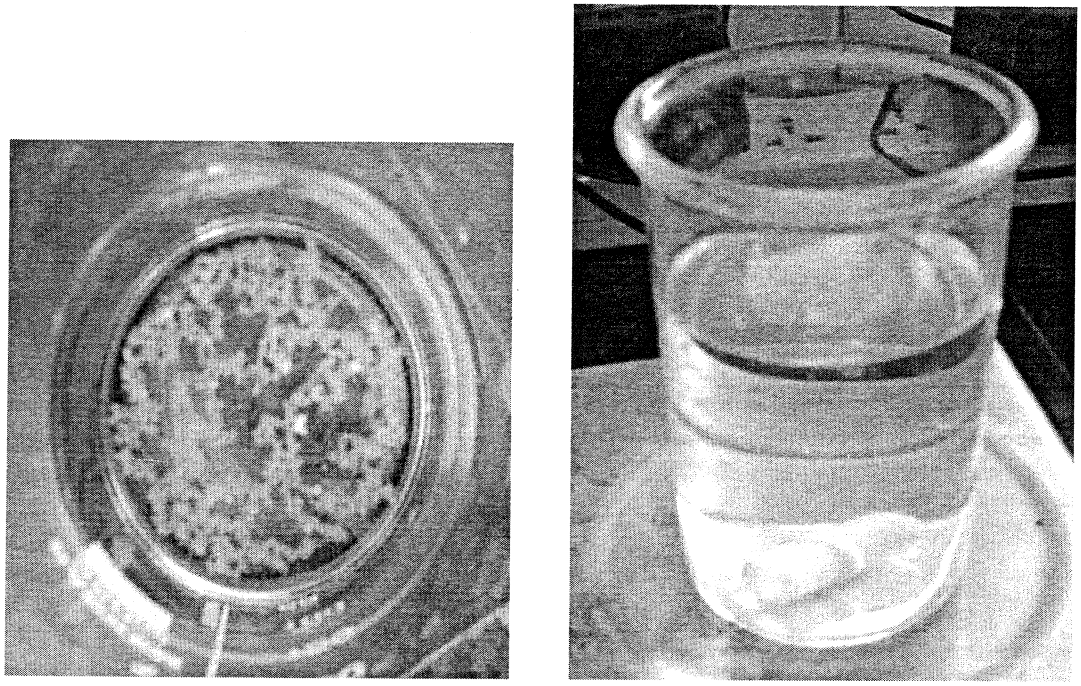
The prepared microballoons were evaluated for drug entrapment by using UV spectroscopy. The percent drug entrapment of Diltiazem HCl in all formulation was found to be good i.e. in the range of 51.61 to 83.97 %. This study was carried out for 12 hours. The microsphere of batch F6 formulation showed an entrapment of 83.97 % containing Drugcoat RS 100 as a release retarding polymer in the ratio of 1:2 to the drug. While the other formulations showed lesser entrapment than this formulation. This can be attributed to the permeation

characteristics of each polymer used, that could facilitate the diffusion of a part of entrapped drug to the surrounding medium during preparation of floating microspheres (See Table 3).

Buoyancy study

The prepared microballoons were subjected to floating test or Buoyancy study. The purpose of preparing floating microspheres is to extend the gastric residence time of a drug. The floating test was carried out to investigate the floatability of the prepared microspheres. The microspheres were spreaded over the surface of SGF i.e. 0.1 N HCl with 0.02% Tween 80 and the fraction of microspheres settled down as a function of time was quantitated. Tween 80 (0.02% w/v), added to SGF, counteracted the downward pulling at the liquid surface by lowering surface tension, because the relatively high surface tension of simulated gastric fluid causes the highest decrease of surface area at the air fluid interface. Floating of microballoons for 12 h was considered satisfactory performance. It was also observed that the microspheres of larger size, showed the longer floating time. It should be noted, however, that the situation *in-vivo* can be quite different and the residence time may vary widely depending on the phase of gastric motility.

All the formulations showed good floating ability. The good buoyancy behavior of the microspheres may be attributed to the hollow nature of the microspheres. Formulation F6 containing Drugcoat RS100 as a release retarding polymer gave the best floating ability (78.66 %) in SGF for 12hrs (See Figure 2 and Table 3).



(a) (b)

Figure 2. Floating behavior of microballoons after 12 Hours (a) Side-view showing microballoons (b) Top-view showing microballoons

Dissolution (In-vitro Drug release) studies

In-vitro release profiles of Diltiazem HCl from all prepared batches of microballoons using different polymer combination was evaluated in 0.1 N HCl (1.2 pH) using USP dissolution apparatus type-I at 37± 0.5^{0}C.

The release of drug from microballoons of batches F1-F3 was containing Diltiazem HCl as model drug and ethyl cellulose (10 CPS) as rate controlling polymer was studied. The drug release was almost linear with time. As the polymer concentration increased the size of microsphere was found to increase and the released rate to decrease. (Shown in Figure 3)

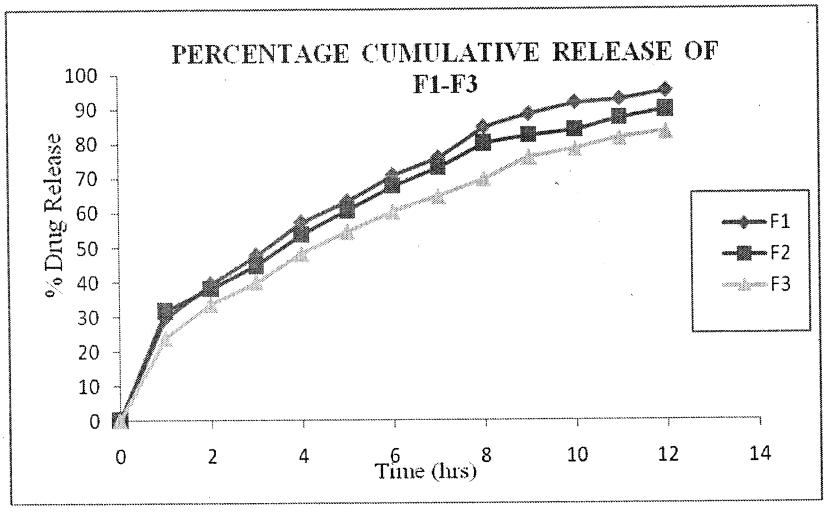


Figure 3. Dissolution profiles of batches EC- (F1-F3)

The release of drug from Microballoons of batches F4-F6 was containing Diltiazem HCl as model drug and Drugcoat RS 100 as a sustained released rate controlling polymer. Released of batch F4 was 99.33% in 9th hour, Batch F5 was 99.01% in 10th hour, and F6 was 97.09% in 12th hour respectively. Drugcoat RS 100 is release rate controlling polymer having low permeability and insoluble in acid medium. It is copolymer of acrylic and methacrylic acid esters with a low content in quaternary ammonium groups and these ammonium groups present as a salts and make the polymer permeable. In the case of batch F4 and F5 complete drug release was obtained in between 9th and 10th hour because of drug present on the surface is released faster and it causes penetration of gastric fluid gives faster release than the F6 batch. Therefore, F6 batch containing Drugcoat RS 100 in the ratio of 1:2 was more suitable for sustained release action (97.09% in 12th hour) than other two batches. (Shown in Figure 4)

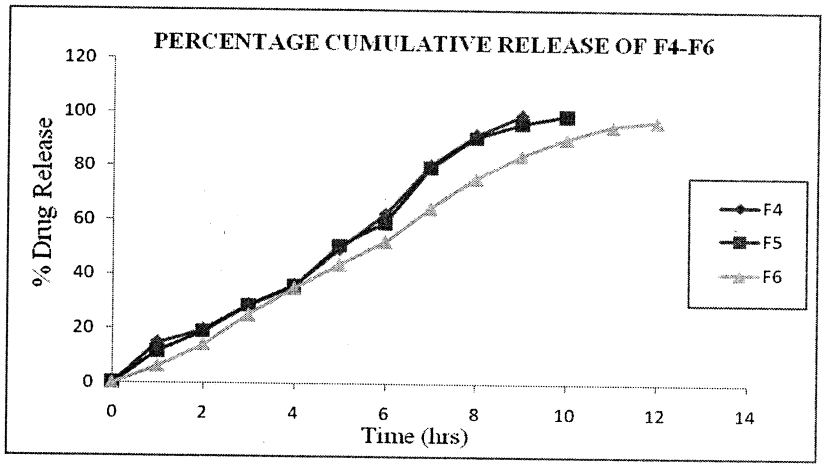


Figure 4. Dissolution profiles of batches DC- RS 100

The release of drug from Microballoons of batches F7-F9 was containing Diltiazem HCl as model drug and Drugcoat RL 100 as a sustained released rate controlling polymer. Drugcoat RL 100 is release rate controlling polymer having high permeability and insoluble in acid medium. It is copolymer of acrylic and methacrylic acid esters with a low content in quaternary ammonium groups and these ammonium groups present as a salts and make the polymer permeable. In the early incubation stage of batch F7, the dissolution rate of Diltiazem HCl was slightly faster especially during the first hour. This was due to the fast dissolution of the drug present on the surface of the microspheres and the rapid penetration of aqueous solution into the microspheres, which is also called burst effect. But in other batches release was linear with time. Released of batch F7 was 98.92 in 7th hour, F8 was 99.65% in 9th hour and F9 batch was 99.54 in 10th hour respectively. These batches released drug much faster than the F4-F6 because it containing the Drugcoat RL 100 as sustained release polymer having high permeability characteristics and the drug is also hydrophilic in nature. (Shown in Figure 5).

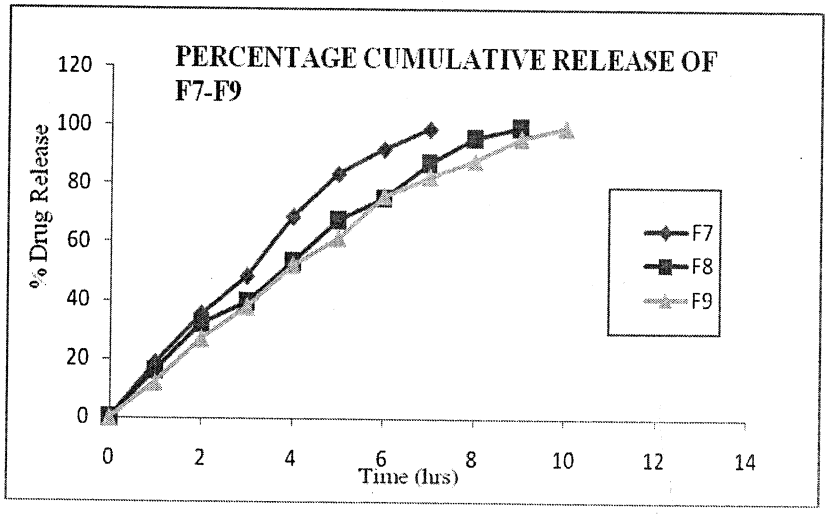
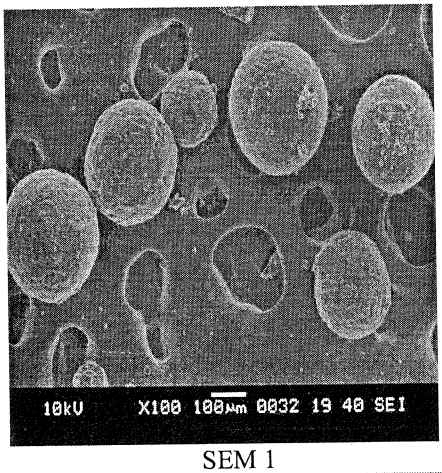


Figure 5. Dissolution profiles of batches DC-RL 100 (F7-F9)

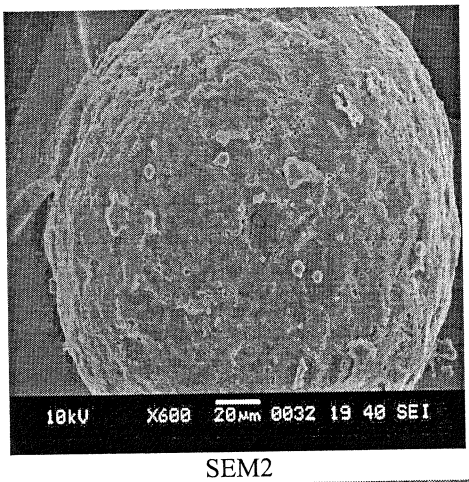
Morphology

Morphology of microballoons of batch F6 was examined by scanning electron microscopy (JEOL 6380A). The smooth surface of such microballoons as seen by SEM might be due to the complete homogeneity of drug and polymers. The outer surface of the microballoons was smooth and dense, while the internal surface was porous. The shell of the microballoons also showed some porous structure. It may be caused by the evaporation of the solvent entrapped within the shell of microballoons after forming a smooth and dense skin layer.

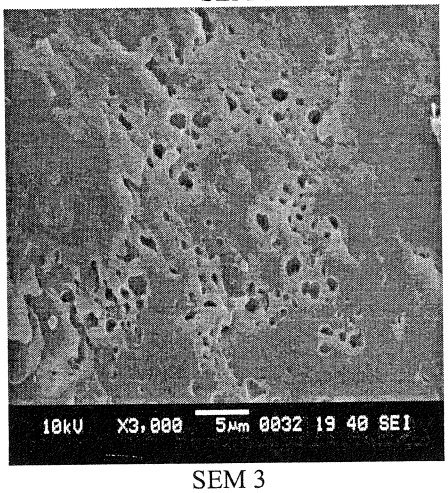
The surface topography revealed a spherical surface for formulation F6 shows round cavity enclosed by an outer shell composed of the drug and polymer. They appeared to be hollow presumably because of the rapid escape of volatile solvent from the polymer matrix. This hollow nature was also responsible for the microspheres floating capability in simulated gastric fluids (Figure 4).



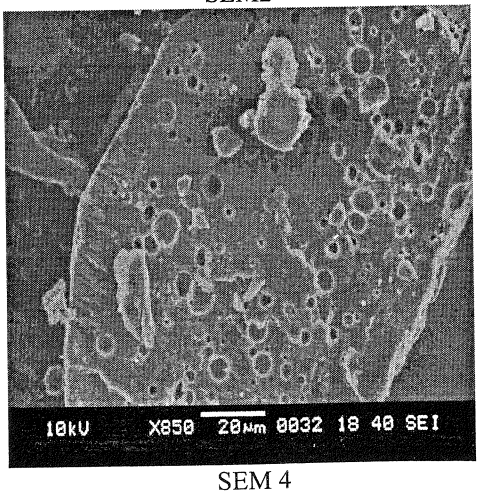
SEM 1



SEM2



SEM 3



SEM 4

Figure 6. SEM 1 size range of Microballoons; **SEM 2** smooth texture of Microballoons; **SEM 3** surface morphology of Microballoons; **SEM 4** Cross section view of Microballoons

Kinetic modeling

The *in-vitro* release data was applied to various kinetic models to predict the drug release kinetics and mechanism. The release constant was calculated from the slop of appropriate plots, and the regression coefficient (r^2) was determined. It was found that the *in-vitro* drug release of microballoons was best explained by Korsmeyer-Peppas model. The correlation coefficient (r^2) was in the range of 0.992-0.998 for various formulations in 0.1N HCl.

The mode of drug release from Microballoons was evaluated using Korsmeyer - Peppas model. The corresponding plot for Korsmeyer - Peppas equation indicated a good linearity in dissolution medium (r^2= 0.996). The value of n was 1.1295 in 0.1N HCl suggested a coupling of the diffusion and erosion mechanism so called super case II transport and indicated that drug release was controlled by more than one process. So, different theories of kinetics were applied to interpret the release rate of Diltiazem HCl from the sustained release floating microballoons of formulation F6. From the coefficient of correlation (R^2) it was found to show that the release of batch F6 is best fit to Korsmeyer-Peppas model (See Table 4).

Stability Study

The selected F6 formulation was subjected to stability studies forl month. At the interval of 15 days the MBs were withdrawn and evaluated for floatability and Drug content study. All the parameters have not shown much variation when compared to the initial data. The *in-vitro* dissolution was carried out for specified time intervals. Based on the results, we observed that, drug release profiles were not affected by exposing to temperature and the specified humidity conditions

Table 4. Estimated values of n and k by regression of log (M_t / M_∞) on log (t)

Batches	Best Fit Model	r	N	k
F1	Matrix	0.997	0.497	28.76
F2	Matrix	0.996	0.458	29.287
F3	Korsmeyer's-Peppas model	0.999	0.521	23.474
F4	First Order	0.992	0.93	11.918
F5	Korsmeyer-Peppas model	0.993	0.999	10.293
F6	Korsmeyer-Peppas model	0.997	1.13	6.8056
F7	Korsmeyer-Peppas model	0.997	0.88	19.12
F8	Korsmeyer-Peppas model	0.997	0.835	16.827
F9	Korsmeyer-Peppas model	0.994	0.914	13.571

Selection of best formulation

Various ratios of ethyl cellulose, Drugcoat RS100 and Drugcoat RL 100 were formulated in the form of batches from F1-F3, F4-F6 and F7-F9 and were subjected to the percent recovery, % buoyancy, % drug entrapment and *in-vitro* dissolution studies for the selection of best formulation batch. However, based on the percent yield, % buoyancy, % drug entrapment and release rate studies of the formulations, it could be concluded that the formulations containing Diltiazem HCl and Drugcoat RS 100 in the ratio of 1:2 i.e. batch F6 (97.09%) released approximately 100% drug over a period of 12 hours. Since it met the all requirement, that's why it was chosen as the best formulation.

Conclusion

The floating drug delivery with sustained release of Diltiazem hydrochloride using various polymers as a carrier in combination with drug was successfully formulated. The prepared MBs of Diltiazem hydrochloride were found to show good micromeritic results, percent recovery, percent buoyancy, drug entrapment and *in-vitro* released. In dissolution study of all formulations it was observed that by increasing concentration of polymers, release rate of drug was retarded. Among which Floating microballoons of F6 batch was found to be satisfactory in terms of all evaluation parameters as it containing Drugcoat RS 100. This batch was found to have better release profile than that of all other formulations. Surface morphology by scanning electron microscopy showed smooth and spherical shape of F6 batch. There was no interaction in drug and polymer. SEM also show good spherical surface. Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention.

Therefore, designed system F6 combining high buoyant ability and suitable drug release rate, could possibly be advantageous in terms of increased bioavailability of Diltiazem HCl. The designed system F6 might be able to float in the stomach. This phenomenon could prolong the gastric residence time (GRT) and delay drug arrival at the absorption site; consequently, the sustained action provided, in addition, microballoons enabled increased drug absorption rate of drug as the microballoons in the stomach gradually sank and arrived at the absorption site. Therefore, multiple unit floating system, i.e., floating microballoons is beneficial with subject to sustain action. The developed formulation overcomes and alleviates the drawbacks and limitations of sustained release preparations. Major advantages of the prepared formulations include- Ease of Preparation, Good Buoyancy, High Entrapment Efficiency, Sustained Release over 12 hours.

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