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Preparation and evaluation of floating multiparticulate drug delivery system

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ABSTRACT

The goal of the present study was to develop a floating mutiparticulate drug delivery system based on gas formation technique, in order to prolong the gastric residence time and increase the overall bioavailability of the drug from dosage form. The system consists of the core pellets which are coated with three different layers, inner layer of drug, middle layer of effervescent material alongwith binder polymer (sodium bicarbonate) and an outermost of gas-entrapped sustained release polymeric membrane (Eudragit® RSPO: RLPO). The time to float increased as the coating level of gas-entrapped polymeric membrane increased. The optimum system could float completely within 2 min. and maintained the buoyancy over a period of 24 h. The drug release was sustained and linear with the square root of time. Increasing coating level of gas-entrapped polymeric membrane decreased the drug release. Both the rapid floating and the sustained release properties were achieved in the floating multiparticulate drug delivery system developed in this current study.

Key words: - Floating, Multiparticulate, Effervescent, Coating, Eudragit.

INTRODUCTION

The ultimate goal of any drug delivery system is effective disease/disorder management, minimum side effects and greater patient compliance in the cost effective manner. The drug therapeutic indices could be maximized while indices of adverse reactions or side effects could be minimized by regulating the drug release in body in a well-defined controlled manner. This would eliminate the haphazard and uncontrolled blood plasma profiles of drugs usually associated with conventional dosage forms Gastro retentive dosage forms, i.e. those designed to

exhibit a prolonged gastric residence time (GRT) have been a topic of interest in terms of their potential for controlled drug delivery.

Gastric residence time (GRT) is one of the important factors affecting the drug bioavailability of pharmaceutical dosage forms [8]. Variable and short gastric emptying time can result in incomplete drug release from the drug delivery system above the absorption zone (stomach or upper part of small intestine), leading to a diminished efficacy of the administered dose [6, 11]. Floating drug delivery system (FDDS) is one of gastroretentive dosage forms which could prolong GRT to obtain sufficient drug bioavailability [1, 2, 25]. The system basically floats in the gastric fluid because of its lower bulk density compared to that of the aqueous medium.

FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine [16, 18]. It is also useful for drugs that act locally in the proximal part of gastrointestinal (GI) tract such as antibiotic administration for Helicobacter pylori eradication in the treatment of peptic ulcer [2, 7, 23, 26] and for drugs that are poorly soluble or unstable in the intestinal fluid [13]. Most of the floating systems previously reported are single unit systems such as tablets and capsules. A drawback of these systems is the high variability of the GI transit time due to their all-or-nothing emptying processes [12, 13, 14, 21, 22, 23]. On the other hand, the multiple-unit dosage forms may be an attractive alternative since they have been shown to reduce the inter- and intra-subject variabilities in drug absorption as well as to lower the possibility of dose dumping [4, 5, 24]. Various multiple-unit floating systems have been developed in different forms and principles such as air compartment multiple-unit system [11], hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method [13, 17, 18], microparticles based on low-density foam powder [20], beads prepared by emulsion–gelation method [19, 22]. Use of swellable polymers and effervescent compounds is another approach for preparing multiple-unit FDDS [12].

In this study, a new multiprticulate FDDS based on gas formation technique was developed. The nonpareils were loaded with drug by solution layering technique followed by coating of the pellets with effervescent component (sodium bicarbonate) using hydroxypropyl methylcellulose (HPMC) as a binder and polymeric membrane of (Eudragit® RSPO and RLPO) as a sustain release membrane respectively, various ratios of the RSPO: RLPO were used. Carvedilol, which is highly absorbed in the upper part of GI tract, was selected as a model drug. The effect of the preparative parameters, e.g., type, blend ratio and coating level of the gas-entrapped polymeric membrane, on the floating ability and drug release properties of the multiparticulatet FDDS were evaluated.

MATERIALS AND METHODS

2.1. Materials

Carvedilol as a gift sample was obtained from Aurobindo pharmaceuticals Ltd. Hyderabad, and was used as a model drug in the present study. Nonpareil seeds were procured from Murli Krishna pharma Pvt. Ltd, Ranjangaon, Pune, HPMC (Methocel® E15LV) was obtained as a gift sample from Dow Chemical, Mumbai. The gas-entrapped polymeric membrane used were polymethacrylates (Eudragit®) RLPO, RSPO were obtained from Rohm Pharma polymers, plasticized with diethyl phthalate (DEP), a water insoluble plasticizer procured from Eastman

Kodak Co., NY, USA, Sodium bicarbonate (Sodium bicarbonate) was used as an effervescent agent with plasticized with polyethylene glycol 400 (PEG 400) as a binder were procured from S D Fine Chemicals, Pune. All other reagents used were of analytical grade.

2.2. Preparation of the multiparticulate FDDS

Table No. I. Blend ratio for preparation of coating solution for RSPO: RLPO

Sr. No	Batch Code	Coating weight gain	Plasticizer Conc. mg (% w/w)	Polymer blend ratio gm (%)		Talc gm (% w/w)	IPA (ml)
				RSPO	RLPO		
1	1a	10 %	600 (10%)	6 (100%)	0(0%)	3 50%)	100
2	1b	15 %	600 (10%)	6 (100%)	0(0%)	3 (50%)	100
3	1c	20 %	600 (10%)	6 (100%)	0(0%)	3 (50%)	100
4	2a	10 %	600 (10%)	4.5 (75%)	1.5 (25%)	3 (50%)	100
5	2b	15 %	600 (10%)	4.5 (75%)	1.5 (25%)	3 (50%)	100
6	2c	20 %	600 (10%)	4.5 (75%)	1.5 (25%)	3 (50%)	100
7	3a	10 %	600 (10%)	3 (50%)	3 (50%)	3 (50%)	100
8	3b	15 %	600 (10%)	3 (50%)	3 (50%)	3 (50%)	100
9	3c	20 %	600 (10%)	3 (50%)	3 (50%)	3 (50%)	100
10	4a	10 %	600 (10%)	1.5 (25%)	4.5 (75%)	3 (50%)	100
11	4b	15 %	600 (10%)	1.5 (25%)	4.5 (75%)	3 (50%)	100
12	4c	20 %	600 (10%)	1.5 (25%)	4.5 (75%)	3 (50%)	100
13	5a	10 %	600 (10%)	0(0%)	6 (100%)	3 (50%)	100
14	5b	15 %	600 (10%)	0(0%)	6 (100%)	3 (50%)	100
15	5c	20 %	600 (10%)	0(0%)	6 (100%)	3 (50%)	100

2.2.1 Preparation of Carvedilol drug layered pellets

Solution layering technique was selected to load drug on the nonpareil seeds (NPS). NPS were dried at 60-70 ºC for 1-2 hours in hot air oven before drug layering and sieved through mesh no.16 & 18 respectively to get the desired size (1.18-1.00mm). 50gm pellets were loaded onto conventional coating pan of 8 " diameter. The solution of Carvedilol was prepared, containing 20 % of overages in Methanol: Ethanol (20:80) & then sprayed on the bed of nonpareil seeds using a pilot type of spray gun, fitted with a 1mm atomizing nozzle (Pharma R & D Coater). After completion of this process, drying of drug loaded NPS was done, drug loaded pellets were dried at 50-60ºC for 1-2 hours in hot air oven.

2.2.2. Coating effervescent layer on the drug loaded pellets.

The drug loaded pellets were coated with two successive layers; an effervescent substance (sodium bicarbonate) as an inner effervescent layer, and polymer blend layer (Eudragit® RSPO andRLPO) as an outer gas-entrapped polymeric membrane. An effervescent agent was incorporated into HPMC solution plasticized with PEG 400 (10%, w/w based on the solids

content of HPMC) and then layered onto the drug loaded pellets. On dry solid basis, the ratios of sodium bicarbonate to HPMC was 8:2 w/w. The coating level of effervescent layer was made up to 12% weight gain was obtained over drug loaded NPS.

The coating solution was sprayed onto the drug loaded pellets in a Pharma R & D Coater. The conditions for layering were, bead charge - 50 g; preheating temperature - 50^0C; preheating time - 15 min, inlet temperature - 50^0C; outlet temperature 40–45^0C; atomizing air pressure, 2 lb/in, spray rate - 0.7 ml/min and pan speed of 20rpm . The Sodium bicarbonate layered pellets were dried in the same coating pan for 30 min at 50^0C to evaporate the residual moisture. The prepared pellets were then removed from the coating chamber and stored in a closed container for further experiments.

The Sodium bicarbonate layered pellets were subsequently coated with polymer blends of Eudragits RSPO: RLPO at varied concentration (100:0, 75:25, 50:50, 25:75 and 0:100) of polymer blend to achieve a weight gain of 10%, 15% and 20% (w/w) respectively. Required quantity (usually 6%w/v found to be optimum due to viscosity restrictions for spraying) of RSPO and RLPO was dissolved in sufficient quantity of organic solvent (Isopropyl alcohol) separately and Dibutyl pthalate (DBP) hydrophobic in nature was selected as plasticizer was dissolved in organic solvent (Isopropyl alcohol) separately. These two solutions were mixed using high speed stirrer, and were allowed to equilibrate with plasticizer for overnight. Talc was added to polymeric solution at a concentration of 50% w/w as a antitacking agent prior to coating on drug loaded pellets. To obtain the complete multiparticulate FDDS, the coating solution was sprayed onto the effervescent layered pellets in a Pharma R & D Coater.

The coating conditions were: bead charge - 15 g; preheating of pan at - 80^0C, preheating time - 15 min, inlet temperature, 45 ◦C; outlet temperature, 40–42 ◦C; atomizing air pressure, 2 lb/in^{-2}; spray rate, 0.5–1 ml/min and pan speed of 20rpm. The pellets were further dried in the coating chamber for 1 hr. after the coating was finished in order to evaporate the residual solvent in the polymeric coatings prior to storage.

2.3. Evaluation of the multiparticulate FDDS

2.3.1.Friability

Friability of all pellet formulations was determined by using USP friability test apparatus. Friability of the pellet formulations was evaluated over 5 gm of samples in Roche Friabilator at 25 rpm for 4 minutes. Prior to and following the test, the weights of the formulation were accurately recorded and the friability ratios were calculated with following equation.
Percent friability (% F) was calculated as follows,

$$\% \ F = \frac{\text{Loss in weight}}{\text{Initial weight}} \ X \ 100$$

A loss of less than 1 % in weight is generally considered acceptable for functional coating.

2.3.2 Bulk Density and Tapped Density:
A quantity of 5 gm of Pellets of each formulation was previously lightly shaken to break any pellet agglomerates formed. This quantity was introduced into a 10 ml measuring cylinder. The pellets were carefully leveled without compacting it, and the apparent volume was measured (V_0). Then cylinder containing sample was tapped using Tap density tester (Veego) for 500 times and the tapped volume was measured to nearest graduated unit. LBD and TBD were calculated using the following formula:

LBD = Weight of the pellets / Volume of packing
TBD = Weight of the pellets / Tapped Volume of the packing.

2.3.3 Hausner ratio:
It provides an indication of the degree of densification which could result from vibration of the feed hopper.

Hausner ratio = Tapped density/ Bulk Density

Lower the Hausner ratio better is the flow property.

2.3.4 Compressibility index:
The compressibility of the granules was determined by Carr's Compressibility Index:

Carr's compressibility index (%) = [(TBD-LBD) X 100] / TBD

Where, TBD (Tapped Bulk Density or Tapped Density),
LBD (Loose Bulk Density or bulk Density)

2.3.5 Content uniformity of coated pellets:
Drug content of different formulations of the coated pellets was estimated in triplicate. 50 mg of the coated pellets were weighed and crushed in mortar and was transferred to 100 ml volumetric flask. To it, 100 ml methanol was added. The solution was stirred for 1 hr. and filtered through Whatman filter paper no.41, after suitable dilution the drug content was determined spectrophotometrically at 243 nm.

2.3.6 Scanning Electron Microscopy (SEM):
The shape and surface characteristics of the pellets were investigated and photographed with help of scanning electron microscopy (JEOL and Tokyo, Japan JSM-6360, Department of Physics, University Pune). Pellets Surface was evaluated before and after coating, at 40X, 45X, 100X & 350 X magnifications.

2.3.7. Floating ability
The floating abilities of the coated effervescent-layered pellets, were determined using 250ml beaker containing 50ml 0.1N HCl. Twenty pellets were placed in the medium; the time required to float and duration for how long they remain floating (floating time) were measured by visual observation. The percentage of floating pellets was calculated by the following equation:

Floating pellets

(FT %) = number of floating pellets at the measure time / Initial number of the pellets × 100

2.3.5. Dissolution study

The USP type-I (rotating basket) dissolution test apparatus (Veego scientific DT 6D). was used to study the drug release from the multiparticulate FDDS at 37.0±0.5 ◦C, 50 rpm using 900 ml of 0.1N HCl. 20 mg equivalent weight of carvedilol pellets were used for dissolution study.5 ml aliquot of the dissolution medium was withdrawn at predetermined time intervals of 0.5 hrs and was replaced by equivalent amount of fresh medium kept at same temperature, aliquot solutions were filtered through Whatman filter paper no.-41. The filtrates were analyzed by UV- visible spectrophotometer at 241 nm. Percent drug released in the sample was determined from the standard calibration curve and cumulative percent drug dissolved was calculated using PCP Disso v2.08 software. The study was performed in triplicate for each formulation.

RESULTS AND DISCUSSION

3.1. *Design of multipleparticulate FDDS*

Fig. I shows the design of multipleparticulate FDDS. The system consisted of core pellet coated with drug, effervescent layer and gas-entrapped polymeric membrane, respectively. Since sodium bicarbonate itself could not adhere onto the core pellets, HPMC was used as a binder in the inner effervescent layer. An ideal coating material for a floating system should be highly water permeable in order to initiate the effervescent reaction and the floating process rapidly. However, the wet or hydrated coatings should also be impermeable to the generated CO2 so as to promote and maintain floatation. Regarding their mechanical properties, the polymeric coatings should be sufficiently flexible in wet state to be able to withstand the pressure of the generated gas and to avoid rupturing. According to these reasons, the higher flexibility polymer, an non aqueous polymer blend (Eudragit® RSPO:RLPO), was chosen and investigated as a gas-entrapped polymeric membrane in this study.

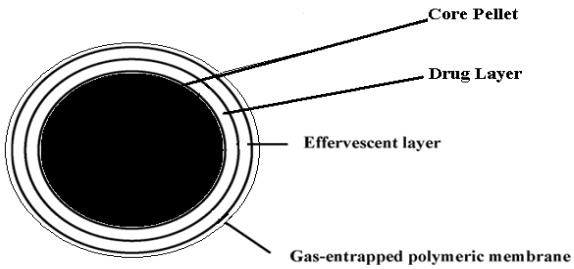


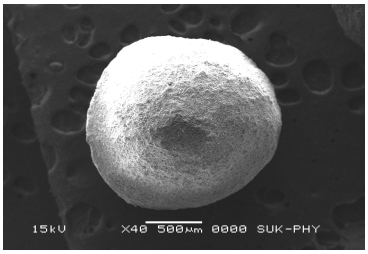
Fig. I. Design of multiple-unit FDDS

Upon contact with the gastric fluid, the fluid penetrates into the effervescent layer through the outer polymeric membrane. Carbon dioxide was liberated via neutralization reaction and was entrapped in the polymeric membrane. After that, the swollen pellets (like balloons) with a density less than 1.0 g/ml and start floating by maintaining the buoyancy. Therefore, the drug

was released from the system for a long time. To develop the multiparticulate FDDS based on gas formation technique, several studies were necessary to identify the formulation variables providing the desired system properties, rapid expansion and formation of low-density system within minutes after contact with gastric fluids and maintaining the buoyancy in stomach with sustained release. The effect of the preparative parameters such as type and coating level of the polymeric membrane, on the floating ability and drug release of the multiple-unit FDDS were evaluated.

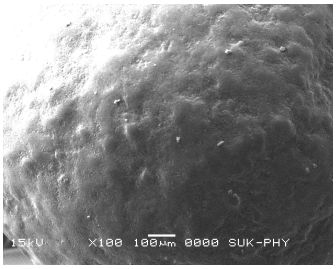
3.2. Pellets characterization

The bulk density values for RS:RL blend formulations was found to be in the range of 0.7748 gm/cm^3 to 0.8048 gm/cm^3 whereas tap density values was found to be in the range 0.8063 gm/cm^3 to 0.9192 gm/cm^3. The values for angle of repose, Hausner ratio, compressibility index were found to be in good correlation indicating that all formulation possess excellent flow property which confirmed free flowing nature of the coated pellets. The results of the content uniformity for RS:RL polymer blend formulations was found to be in the range 95.80 ± 0.01 % to 98.37 ± 0.014 %.The friability of the formulation was 0.17±0.04%. This indicated that the core pellets were quite hard and able to withstand the mechanical stresses of the subsequent coating process. Fig. II(a) shows the appearance of the external morphology of the core pellet under SEM. The core pellets were spherical agglomerates with a slightly rough surface. The surface of the effervescent-layered pellet was slightly smoother (Fig. II(b)) and the smoothest was the surface of effervescent-layered pellet coated with polymeric membrane (Eudragit® RSPO: RLPO) (Fig. II(c).



(a)

(b)



(c)

Fig. II. Scanning electron micrographs of the surfaces of the core pellets, effervescent layered pellet (HPMC:NaHCO3; 2:8 w/w) and effervescent-layered pellet coated with

Eudragit® RSPO: RLPO magnification 100×. Key: (a) core pellet, (b) effervescent-layered pellet, and (c) effervescent-layered pellet coated with Eudragit® RSPO: RLPO

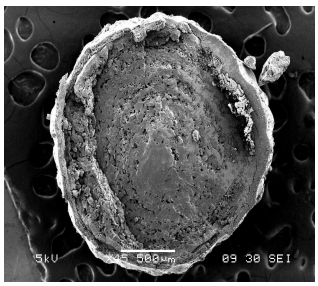


Fig. III. Scanning electron micrographs of cross sectional area of optimized formulation.

The coating layer of the pellet formulations were observed with the cross sectional observation of pellets with SEM, showing the core in the center and outer three coating layers levels towards the outside as shown. (Figure No. III)

3.3. Floating ability

Table No. II: Floating characteristics of pellets

Code	Floating lag time(Minutes)	Floating Time (Hrs)
1a	>60	≈1.5hr
1b	>60	≈1.5hr
1c	>60	≈1.5hr
2a	≈1	>24hr
2b	≈1.5	>24hr
2c	≈2	>24hr
3a	≈1	>24hr
3b	≈1.5	>24hr
3c	≈2	>24hr
4a	≈0.5	>24hr
4b	≈1	>24hr
4c	≈1	>24hr
5a	≈0.5	>24hr
5b	≈0.5	>24hr
5c	≈0.5	>24hr

The floating ability of the effervescent-layered pellets coated with polymeric membrane (complete multipleparticulate FDDS) were investigated in respect to ratio and level of the

polymeric coating. The system should float in a few minutes after contact with gastric fluid to prevent the dosage form from transiting into the small intestine together with food [11]. The coating level of effervescent layer was kept constant at 12% (w/w). The prolonged floating time in the pellets layered with lower amount Sodium bicarbonate was attributed to higher amount of HPMC which possessed higher entrapment capacity of the generated CO2. The floating time of only effervescent-layered pellets was quite short (less than 0.5 h) because HPMC dissolved and there was no polymeric membrane which could entrap the generated CO2 gas. Therefore, the complete multiparticulate FDDS (effervescent-layered pellets coated with polymeric membrane) was prepared and evaluated for floating ability. Blends of Eudragit® RSPO and RLPO were used as polymeric membrane. The multiparticulate FDDS using Eudragit® RSPO: RLPO (75:25) with 15% of weight gain for polymeric membrane floated completely within 1 min. The time to float of the systems increased with increasing level of polymeric membrane coating and with increasing level of Eudragit® RSPO due to the delayed water penetration through the matrix coating. The duration of floating was longer than 24 h. It was indicated that Eudragit® RLPO polymeric membrane was impermeable to the generated CO2 and could maintain the floatation. The multiparticulate FDDS systems coated with Eudragit® RSPO: RLPO (100:0) blend as polymeric membrane, floats only for 1.5hr with coating level (10%, 15% and 20% weight gain). Eudragit® RSPO might not be permeable enough for dissolution medium to induce the effervescent reaction and generate sufficient amount of CO2 to make the pellets floated. Eudragit® RLPO is a highly water permeable polymer according to its higher quaternary ammonium groups, in the structure [3, 10] and is more hydrophilic than Eudragit® RSPO. It therefore hydrated faster and resulted in a shorter time to float [15]. Based on these results, Eudragit® RSPO: RLPO blends (75:25) was the polymer blend of choice as gas-entrapped membrane in this multiple-unit FDDS

3.4. In vitro drug release characteristics

The release of carvedilol from the insoluble matrix core pellets may be described by the following equation:

$$Mt/M\infty = Kt\ 1/2$$

where $Mt/M\infty$ is the percentage of drug released at time t and k is a release constant which reflects: (a) the shape of the matrix, (b) the internal structure of the matrix as it affects the tortuosity and porosity of the matrix and (c) the drug concentration and solubility [9]. It is applicable if the release of drug is largely governed by diffusion through water-filled pores in the matrix.

Fig. IV. shows that the release of carvedilol from the effervescent-layered pellets coated with Eudragit® RSPO:RLPO as polymeric membrane conforms to Eq. with the correlation coefficient (r2) of more than 0.97 in each case. The drug release of the effervescent-layered pellets coated with Eudragit® RLPO was lower than that of the uncoated effervescent-layered pellets because the polymeric membrane retarded the water penetration through the effervescent-layered cores. The drug release tended to increase with increasing amount of Eudragit® RLPO in polymer blend. The effects of polymer blend type and coating level on drug release were also investigated.

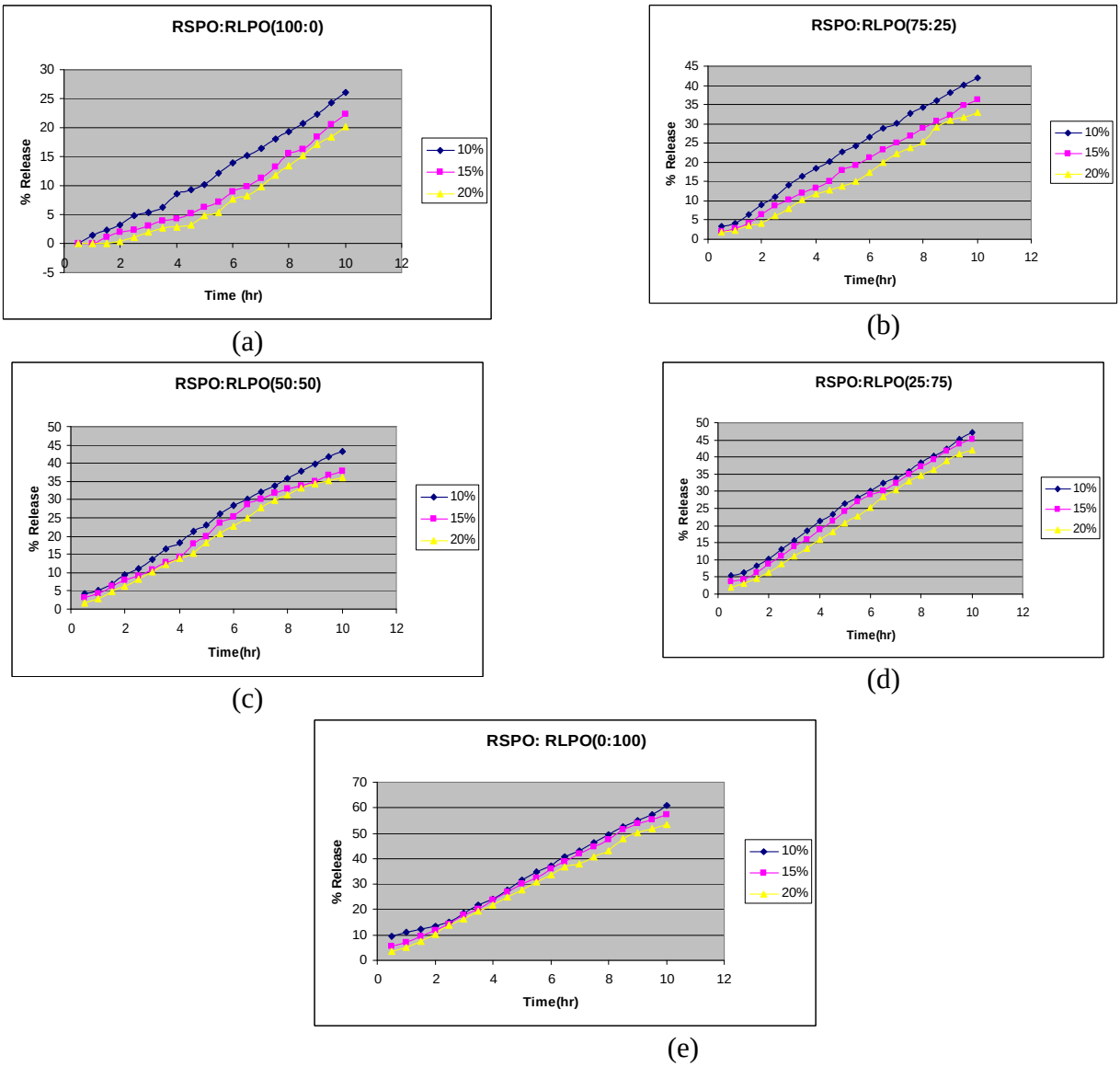


Fig. IV. The release of carvedilol from effervescent-layered pellets coated with Eudragit® RSPO: RLPO (a)100: 0, (b)75:25, (c) 50:50, (d)25:75, (e)0:100 as polymeric membrane in 0.1N HCl, plotted as the cumulative percentage of drug released vs. time. The means of triplicate data are plotted.

Fig. 4 shows drug release results of multiprticulate FDDS with various types of blends of Eudragit® RSPO: RLPO. The drug release decreased with increasing level of polymeric coating from 10 to 20%. The higher membrane thickness retarded water penetration, resulting in decreasing drug release [12, 15]. The drug release from the system using Eudragit® SPO: RLPO (75:25)15% as gas-entrapped polymeric membrane was linear with the time. For high water permeability of Eudragit® RLPO, the release profile of the multiparticulate FDDS seems to be dominated by drug diffusion through the polymer matrix from the core pellets instead of drug diffusion through polymeric membrane of reservoir system.

CONCLUSIONS

The multiparticulate FDDS based on gas formation technique was developed. The system consists of nonpareils coated with drug, effervescent layer and polymeric membrane. The floating ability and drug release of the system were dependent on blend type and coating level of the polymeric membrane. The system using blend ratio of Eudragit® RLPO: RSPO(0:100) could not float because Eudragit® RSPO might not be permeable enough for dissolution medium to induce the effervescent reaction and generate sufficient amount of CO2 to make the pellets floated The system using blend ratio of Eudragit® RLPO: RSPO(100:0,75:25,50:50 and 25:75) as a polymeric membrane could float as Eudragit® RLPO had high water and low CO2-permeabilities with high flexibility. The system could float completely within 3 min and maintain the buoyancy over a period of 24 h. The multiparticulate FDDS with rapid floating and sustained drug release was obtained and could be a promising gastroretentive DDS.

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REFERENCES

[1] S. Arora., J. Ali, A. Ahuja, R. K Khar, S. Baboota, *AAPS Pharm. Sci. Technol*., **2005**, article 47.
[2] P. L. Bardonnet, V. Faivre, W.J. Pugh, J. C. Piffaretti, F. Falson, *J. Contr. Release*., **2006**, 111, 1–18.
[3] K.H. Bauer, K. Lehmann, H. P. Osterwald, G. Rothgang, Medpharm Scientific Publishers., **1998**, pp. 63–119.
[4] H. Bechgaard, K. Ladefoged. *J. Pharm. Pharmacol*., **1978**, 30, 690–692.
[5] H. Bechgaard, , G. H. Nielson, *Drug Dev. Ind. Pharm*., **1978**, 4, 53–67.
[6] H. R Chueh, H. R. Zia, C. T. Rhodes, *Drug Dev. Ind. Pharm*., **1995**, 21, 1725–1747.
[7] M. P. Cooreman, P. Krausgrill, K. J. Hengels, *Antimicrob. Agents Chemother*., **1993**, 37, 1506–1509.
[8] S. Desai, S. Bolton. *Pharm. Res*., **1993**, 10, 1321–1325.
[9] J.L Ford, K. Mitchell, P. Rowe, D. J. Armstrong, P. N. C Elliott, C. Rostron, J. E. Hogan. *Int. J. Pharm*., **1991**, 71, 95–104.
[10] I. Ghebre-Sellassie, R. U. Nesbitt, J. Wang. Marcel Dekker, New York, **1997**, 2nd ed, pp. 267–286.
[11] V. Iannuccelli, G. Coppi, M. T. Bernabei, R. Cameroni. *Int. J. Pharm.*, **1998**, 174, 47–54.
[12] M. Ichigawa, S. Watanabe, Y. Miyake. *J. Pharm. Sci*., **1991**, 80, 1062–1066.
[13] S. K. Jain, A. M. Awasthi, N. K. Jain, G. P. Agrawal. **2005**, *J. Contr. Release*., 107, 300–309.
[14] Y. Kawashima, T. Niwa, H. Takeuchi, T. Hino, Y. Ito. *J. Contr. Release*., **1991**, 16, 279–290.

[15] I.Krogel, R. Bodmeier. *Int. J. Pharm*., **1999**, 187, 175–184.
[16] N. Rouge, P. Buri, E. Doelker. *Int. J. Pharm*., **1996**, 136, 117–139.
[17] Y. Sato, Y. Kawashima, H. Takeuchi, H. Yamamoto. *Eur. J. Pharm. Biopharm*., **2003**, 55, 297–304.
[18] Y. Sato, Y. Kawashima, H. Takeuchi, H. Yamamoto. *Int. J. Pharm*., **2004**, 275, 97–107.
[19] P. Sriamornsak, N. Thirawong, S. Puttipipatkhachorn. *Eur. J. Pharm., Sci.* **2005**, 24, 363–373.
[20] A. Streubel, J. Siepmann, R. Bodmeier. *Int. J. Pharm*., **2002**, 241, 279–292.
[21] A. Streubel, J. Siepmann, R. Bodmeier. *J. Microencapsul*., **2003**, 20, 329–347.
[22] R. Talukder, R. Fassihi. *Drug Dev. Ind. Pharm*., **2004**, 30, 405–412.
[23] R.B Umamaheshwari, S. Jain, D. Bhadra, N. K. Jain. *J. Pharm. Pharmacol*., **2003**, 55, 1607–1613.
[24] A. Vervaet, L. Baert, J. P Remon. *Int. J. Pharm*., **1995**, 116, 131–146.
[25] L. Whitehead, J. T Fell, J. H. Collett, H.L. Sharma, A. M. Smith. *J. Contr. Release*., **1998**, 55, 3–12.
[26] L. Yang, , J. Eshraghi, R. Fassihi. *J. Contr. Release*., **1999**, 57, 215–222.