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DEVELOPMENT, DESIGN AND EFFECTS OF FORMULATION AND PROCESSING PARAMETERS ON DRUG RELEASE OF FLOATING MATRIX TABLETS USING LOW DENSITY POWDER

***Basanta Kumar Behera[1], Ranjit Mohapatra[1], Sunit Kumar Sahu[1], Monalisha Panigrahi[2], Manasi Khadanga[2]**

[1]University Department of Pharmaceutical Sciences, Utkal University,Vani Vihar, India

[2]Jeypore College of Pharmacy, Rondapalli, Jeypore, Koraput,Odisha, India

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***Correspondence for Author:**

*** Basanta Kumar Behera**

University Department of Pharmaceutical Sciences, Utkal University,Vani Vihar, India

basanta77behera@gmail.com

ABSTRACT

Recent approaches to increase the gastric residence time of drug delivery systems include bioadhesive devices, systems that rapidly increase in size upon swallowing and low density devices that float on the gastric contents. To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (approximately 1.004 g/cm^3).

The objectives of the present study were to develop a single unit, floating drug delivery system consisting of low density polypropylene foam powder, matrix-forming polymer(s), drug, and filler (optional), and to study the effect of important formulation and processing parameters on the floating and drug release behavior of these systems. The highly porous foam powder provided low density and, thus, excellent in vitro floating behavior of the tablets. All foam powder-containing tablets remained floating for at least 8 h in 0.1 N HCl at 37^{0}C. Different types of matrix-forming polymers were studied. The tablets eroded upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion for the resulting release patterns varied significantly with the type of matrix former. The release rate could effectively be modified by varying the matrix-forming polymer/foam powder ratio, the initial drug loading, the tablet geometry , the type of matrix-forming polymer, the use of polymer blends and the addition of water-soluble or water-insoluble fillers (such as lactose or microcrystalline cellulose). The floating behavior of

the low density drug delivery systems could successfully be combined with accurate control of the drug release patterns.

Key Words: Floating drug delivery, matrix tablets, in vitro evaluations.

INTRODUCTION

Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for drugs (i) that are locally active in the stomach, (ii) that have an absorption window in the stomach or in the upper small intestine, (iii) that are unstable in the intestinal or colonic environment, and/or (iv) have low solubility at high pH values. In addition, as the total gastrointestinal transit time of dosage forms is increased by prolonging the gastric residence time, these systems can also be used as sustained release devices with a reduced frequency of administration and, therefore, improved patient compliance. Recent approaches to increase the gastric residence time of drug delivery systems include (i) bioadhesive devices, (ii) systems that rapidly increase in size upon swallowing, and (iii) low density devices that float on the gastric contents. Floating drug delivery systems were first described by Davis in 1968. When the floating matrix tablets containing gas-generating agents were exposed to HCl, hydrochloric acid reacted with sodium bicarbonate in the floating tablet inducing CO_2 formation. The generated gas was entrapped into the matrix of swollen polymer matrix and well protected by gel formed by hydration of polymers, which led to floating of the dosage forms. To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (approximately 1.004 g/cm^3). [1-9]

The objectives of the present study were to develop a single unit, floating drug delivery system consisting of low density polypropylene foam powder, matrix-forming polymer(s), drug, and filler (optional), and to study the effect of important formulation and processing parameters on the floating and drug release behavior of these systems.

MATERIALS

Chlorpheniramine maleate (CPM) , Diltiazem hydrochloride (DHL) , Theophylline anhydrous and Verapamil hydrochloride were obtained as a gift sample from M/S. Japson Pharmaceuticals Ltd.Sangrur, India; Modimundi Pharma Ltd, Modipuram, India; M/S. Lupin Pharmaceuticals Ltd., Aurangabad, India and M/S.Torrent Research Centre, Gandhinagar,India respectively. Polypropylene foam powder, hydroxypropyl methylcellulose, carrageenan, corn starch, gum guar, gum Arabic, polyacrylic acids, Carbopol 971P, Carbopol 974P, Noveon AA1 (polycarbophil), sodium alginate, dibasic calcium phosphate (Emcompress) , lactose, microcrystalline cellulose (Avicel PH-101) and

magnesium stearate are purchased from market (Loba chemicals and S. D. Fine Chemicals Ltd., Mumbai, India). The all other reagents were of analytical grade.

METHODS

Tablet preparation

Tablets containing 0.5% w/w magnesium stearate as lubricant were prepared by direct compression. The respective powders [drug, foam powder, polymer(s) and optional additives, compositions listed in Table 1 were blended thoroughly with a mortar and pestle. 8–505 mg of the mixture was weighed and fed manually into the die of an instrumented single-punch tableting machine to produce tablets using flat- faced punches (2, 9, 12, or 16 mm in diameter). hardness of the tablets was kept constant.

Table 1: Compositions of the tablets

	Formulation No*.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Verapamil HCl	120	120	120	-	-	-	18	36	108	180	42	92	168	3	53	157	120	120	120	120
CPM	-	-	-	120	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diltiazem HCl	-	-	-	-	120	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Theophylline	-	-	-	-	-	120	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HPMC K15M	240	150	60	150	150	150	25	23	162	90	52	115	210	3	66	196	-	-	-	100
HPMCE50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	150	-	-	-
HPMCE5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	150	-	-
Carbopol 934P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	150	-
Lactose	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	50
Foam powder	-	90	180	90	90	90	90	90	90	90	31	69	126	2	40	118	90	90	90	90
Density (gm/cm^3)	1.02	0.87	0.72	0.94	0.90	0.93	0.86	0.86	0.87	0.89	0.85	0.93	0.85	0.98	0.96	0.89	0.89	0.89	0.99	0.93

	Formulation No*.																		
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Verapamil HCl	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120
HPMC K15M	100	100	50	75	20	20	20	20	20	20	20	20	20	40	30	-	40	30	-
Carbopol 934P	-	-	-	-	30	-	-	-	-	-	-	-	-	10	20	50	-	-	-
Carbopol 974P	-	-	-	-	-	30	-	-	-	-	-	-	-	-	-	-	-	-	-
Carbopol 971P	-	-	-	-	-	-	30	-	-	-	-	-	-	-	-	-	-	-	-
Noveon AA1	-	-	-	-	-	-	-	30	-	-	-	-	-	-	-	-	-	-	-
Na-alginate	-	-	-	-	-	-	-	-	30	-	-	-	-	-	-	-	10	20	50
Corn starch	-	-	-	-	-	-	-	-	-	30	-	-	-	-	-	-	-	-	-
Carrageenan	-	-	-	-	-	-	-	-	-	-	30	-	-	-	-	-	-	-	-
Gum guar	-	-	-	-	-	-	-	-	-	-	-	30	-	-	-	-	-	-	-
Gum arabic	-	-	-	-	-	-	-	-	-	-	-	-	30	-	-	-	-	-	-
Lactose	-	-	100	75	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
MCC	50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Emcompress	-	50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Foam powder	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90
Density (gm/cm^3)	0.89	0.93	0.90	0.93	0.87	0.92	0.92	0.91	0.92	0.94	0.91	0.93	0.93	0.88	0.88	0.85	0.90	0.91	0.92

* F1 means Formulation No 1 and so on

Floating behavior of the tablets

The in vitro floating behavior of the tablets was studied by placing them in 500 ml plastic containers filled with 300 ml preheated 0.1 N HCl (pH 1.2, 37^0C), followed by horizontal shaking for 8 h (37^0C, 75 rpm, *n*=3). The floating lag times (time period between placing the tablet in the medium and tablet floating) and floating durations of the tablets were determined by visual observation.

***In vitro* drug release**

In vitro drug release studies were conducted by placing the tablets in 500 ml plastic containers filled with 300 ml preheated release medium (0.1 N HCl, pH 1.2, 37^0C), followed by horizontal shaking for 8 h (37^0C, 75 rpm, *n*=3). The amount of drug released was detected UV-spectrophotometrically at the following wave- lengths: CPM, λ= 264 nm; diltiazem HCl, λ= 236 nm; theophylline ,λ= 270 nm; verapamil HCl , λ= 278 nm.

Density measurements

The apparent densities of the tablets were calculated from their volumes and masses (*n*=6). The volumes *V* of the cylindrical tablets were calculated from their heights *h* and radii *r* (both determined with a micrometer gauge) using the mathematical equation for a cylinder ($V= \pi$ X r^2 X h). The density of 0.1 N HCl at 37^0C was determined with a pycnometer (*n*=3).

RESULTS AND DISCUSSION

Floating behavior

Incorporation of the highly porous foam powder in the matrix tablets provides densities that are lower than the density of the release medium [0.69–0.98 g/ cm^3 (Table1 and Figure 1), compared with 1.00 g/ cm^3 for the release medium]. 17% w/w foam powder (based on the mass of the tablet) was sufficient to achieve proper in vitro floating behavior for at least 8 h.

In contrast to most conventional floating systems (including gas-generating ones), these tablets floated immediately upon contact with the release medium, showing no lag times in floating behavior because the low density is provided from the beginning (*t* = 0). Extended floating times are achieved due to the air entrapped within the foam powder particles, which is only slowly removed from the system upon contact with the release medium.

As expected, tablets without polypropylene foam powder (e.g., consisting of 240 mg HPMC K15M and 120 mg verapamil HCl) first sank before floating, showing floating lag times of

between 9 and 33 min. Replacing only 8% w/w (based on the mass of the tablet) of the HPMC with the foam powder reduced the lag times to 2 min.

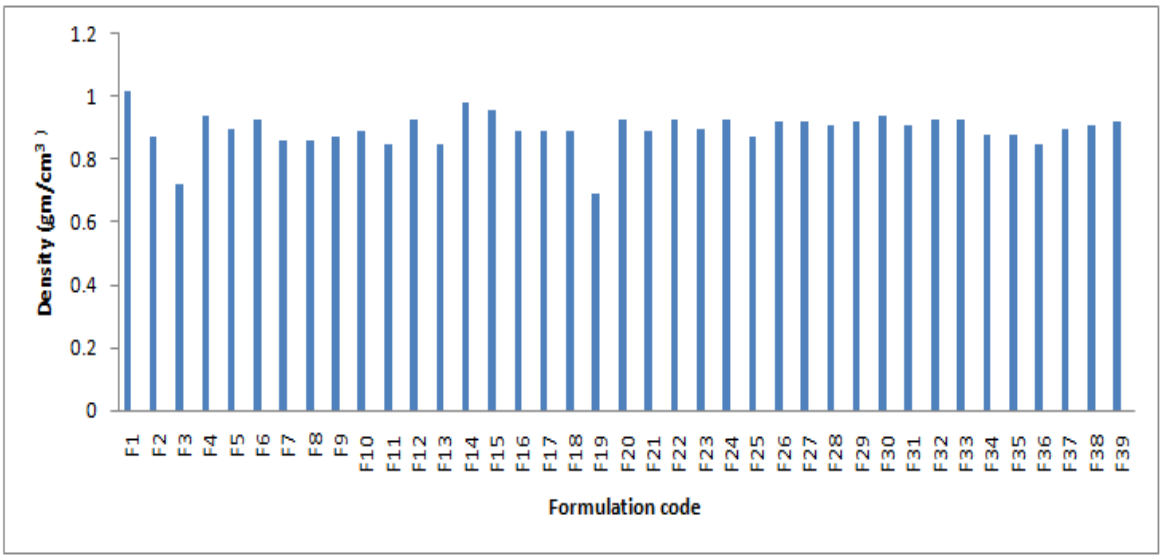

Figure 1: Densities of different formulations

***In vitro* drug release**

i. Effect of the ‘‘HPMC K15M/ Polypropylene foam powder’’ ratio

The drug release decreased when reducing the amount of foam powder from 180 to 0 mg and simultaneously increasing the amount of HPMC K15M from 60 to 240 mg (keeping the amount of drug constant: 120 mg) (Figure 2). This can probably be attributed to the different properties of the polymer networks through which the drug must diffuse. Polypropylene can be regarded as impermeable for the drug (extremely low drug diffusion coefficients). Thus, drug diffusion is restricted to water-filled pores within the foam powder particles and to the swollen HPMC hydrogel. With decreasing amounts of HPMC, the density of the swollen hydrogel network decreases, presenting less hindrance for drug diffusion. Consequently, the drug release rates increase. The shape of the observed drug release curves from foam powder-containing and foam powder free tablets is very similar, which indicates that the swollen hydrogel network and not the foam powder predominantly controls drug release.

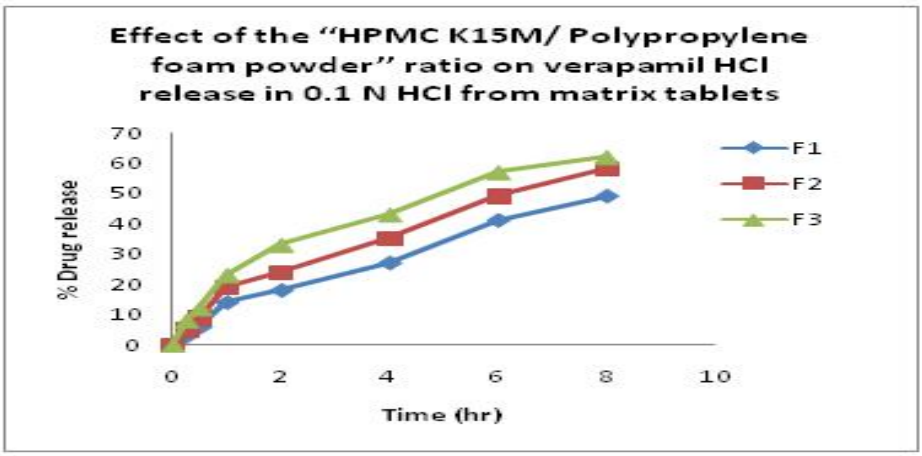

Figure 2: Effect of the ''HPMC K15M/ Polypropylene foam powder'' ratio on Verapamil HCl release in 0.1 N HCl from matrix tablets

ii. Effect of the type of drug and initial drug loading

Drug release strongly depended on the type of drug, decreasing in the rank order CPM > diltiazem HCl > verapamil HCl ≈ theophylline (Figure 3A). The reasons for these differences are not straightforward and can probably be related to various overlapping factors, such as (i) the solubilities of the drugs within the bulk fluid [574, 588, 392 and 15.4 mg/ml in 0.1 N HCl at 37^0C for CPM, diltiazem HCl, verapamil HCl and theophylline respectively [10-13]], (ii) drug molecular weights [274.79, 414.53, 454.61 and 180.17 Da for CPM, diltiazem, verapamil and theophylline, respectively [14-15]], which affect the drug diffusivities within the swollen polymeric networks, (iii) the drug dissolution rates, and (iv) polymer–drug interactions.

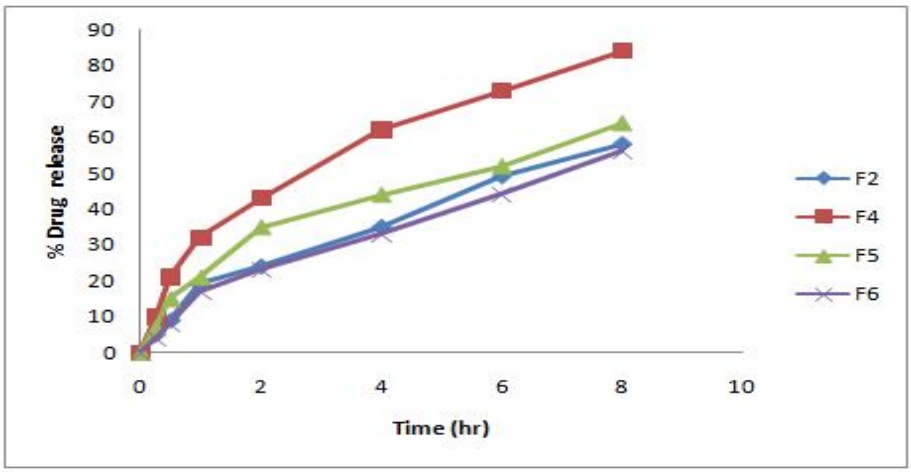

Figure 3A: Effect of the type of drug (initial radius 6 mm, 360 mg tablet weight/120 mg drug, 150 mg polymer, 90 mg polypropylene foam powder; compositions in Table1, formulation Nos. 2, 4, 5 and 6)

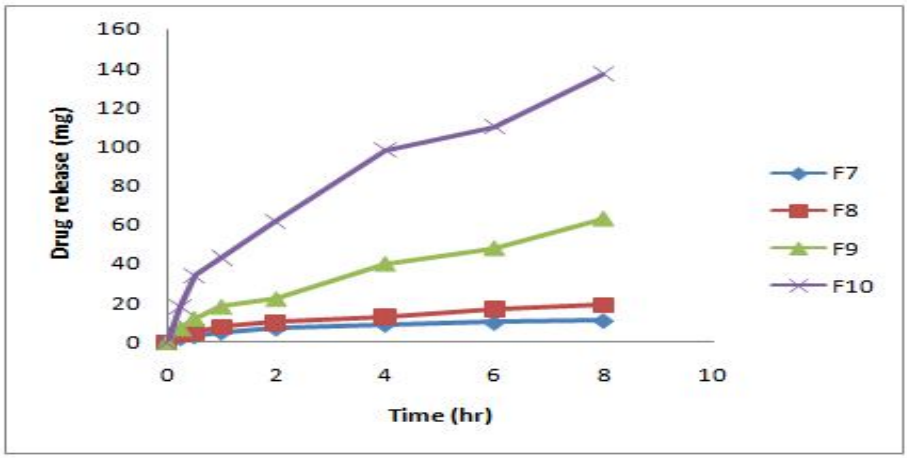

Figure 3B: Effect of the initial Verapamil HCl loading (initial radius 6 mm, 360 mg tablet weight; compositions in Table1, formulation Nos. 7 to 10) on the release patterns from HPMC K15M-based floating matrix tablets in 0.1 N HCl.

The initial drug loading of the low density matrix tablets significantly affected the resulting drug release rate in 0.1 N HCl (Figure 3B). The release rate, both in mg/time unit and in % / time unit (data not shown), increased with increasing drug content. This can again be explained by the different properties of the swollen hydrogel networks. At 5% w/w drug loading, the tablet consists mainly of HPMC (70% w/w). Thus, upon water imbibition a relatively tight macromolecular network results, presenting a significant hindrance for drug diffusion. With increasing drug loadings, the relative HPMC content decreases and, thus, the tightness of the swollen hydrogel network decreases. Consequently, the drug diffusivity and release rate increase.

iii. Effect of the tablet geometry

A simple, but very effective tool for modifying the release kinetics from matrix tablets is to vary their geometry. Varying the initial radius and height of cylindrical tablets strongly affects the resulting drug release rate, which can be predicted theoretically. The release rate of verapamil HCl from HPMC K15M-based devices with 25% w/w foam powder and 33% w/w drug loading as a function of initial tablet height (1.3–5.2 mm at a constant tablet radius of 6 mm) is shown in Figure 4A. The absolute release rate of the drug increased with increasing tablet height. This can be attributed to the higher absolute verapamil HCl amounts incorporated within the system with increasing matrix volume. When plotting the respective relative amounts of drug released in percent versus time, it can be seen that the relative drug

release rate decreases with increasing tablet height (data not shown). This can probably be explained by the decreasing relative surface area of the matrices with increasing tablet height.

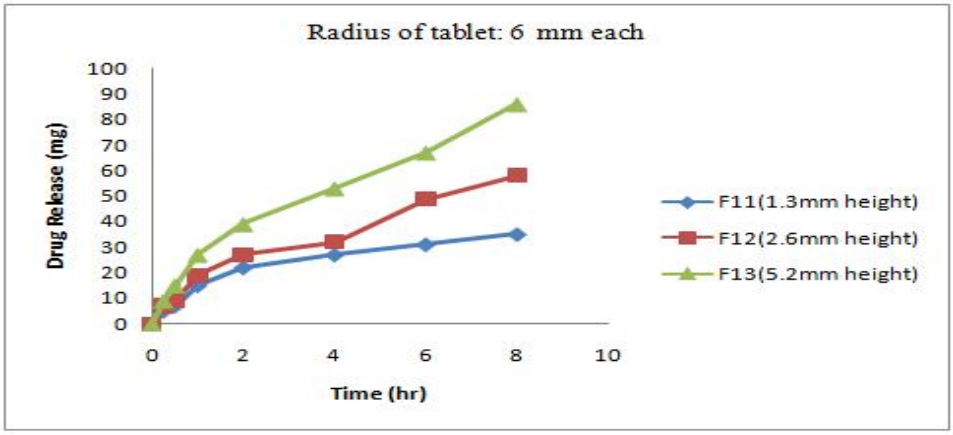

Figure 4A: Effect of tablet geometry (height) on verapamil HCl release from HPMC K15M-containing floating matrix tablets in 0.1 N HCl. Effect of tablet height (initial tablet radius 6 mm, initial tablet height given in the figure, 33% w/w initial drug loading, 25% w/w polypropylene foam powder; compositions in Table1, formulation Nos. 11 to 13).

The tablet radius (1.0–8.0 mm at a constant tablet height of 2.6 mm) also had a very pronounced effect on the absolute drug release rate (Figure 4B). With increasing initial tablet radius, the volume of the system and, thus, the amount of drug available for diffusion increases, resulting in increased absolute amounts of drug released. In contrast, the relative surface area of the device decreases, and the amount of drug released in %/time unit decreased (data not shown).

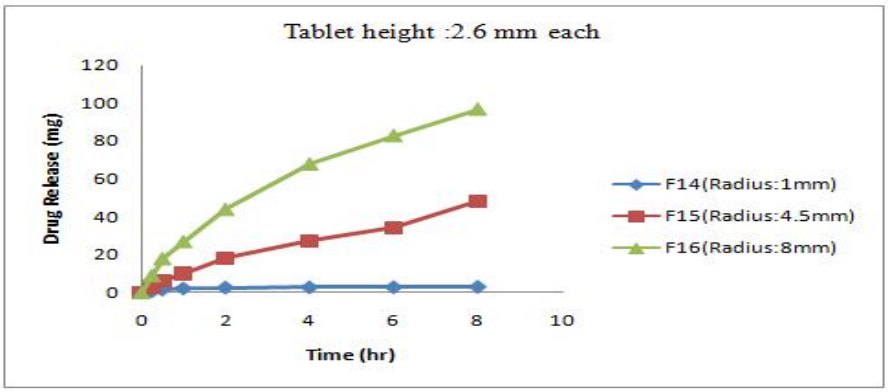

Figure 4B: Effect of tablet geometry (radius) on verapamil HCl release from HPMC K15M-containing floating matrix tablets in 0.1 N HCl. Effect of tablet radius (initial tablet height 2.6 mm, initial tablet radius given in the figure, 33% w/w initial drug loading, 25% w/w polypropylene foam powder; compositions in Table1, formulation Nos. 14 to 16).

iv. Effect of type of matrix-forming polymer

The effect of the type of matrix polymer (HPMC E5, HPMC E50, HPMC K15M, or Carbopol 934P) used for the preparation of floating, low density tablets on the resulting drug release kinetics is shown in Figure 5. The three HPMC types / grades differ in the type of substitution and/or molecular weight (which can be correlated with the polymer viscosity): Methocel E and K contain 28–30 and 19–24% methoxyl groups; the viscosities of 2% aqueous solutions of HPMC E5, E50 and K15M at 20^0C are 5, 50, and 15,000 cps, respectively. The drug release rate decreased in the rank order HPMC E5>HPMC E50>HPMC K15M>Carbopol 934P. This can probably be attributed to the different diffusion and swelling behavior in /of these polymers.

With increasing macromolecular weight, the degree of entanglement of the polymer chains increases. Thus, the mobility of the macromolecules in the fully swollen systems decreases. According to the free volume theory of diffusion, the probability for a diffusing molecule to jump from one cavity into another, hence, decreases. This leads to decreased drug diffusion coefficients and decreased drug release rates with increasing molecular weights. In addition to the effect on the polymer swelling behavior, the increase in polymer molecular weight also modifies the polymer dissolution behavior. With increasing macromolecular weight the dissolution rate decreases, thus the drug release decreases. The different polymer dissolution behaviors could be observed visually by the release of the low density polypropylene foam powder. Clearly, the dissolution of HPMC E5-containing tablets was faster than that of HPMC E50-based systems. Polypropylene foam powder release from HPMC K15M-containing tablets was very slow, and practically no foam powder was released from the Carbopol 934P-based system during the observation period. This can be explained by the different chemical structures of the polymers (substitution patterns, type of polymer backbones).

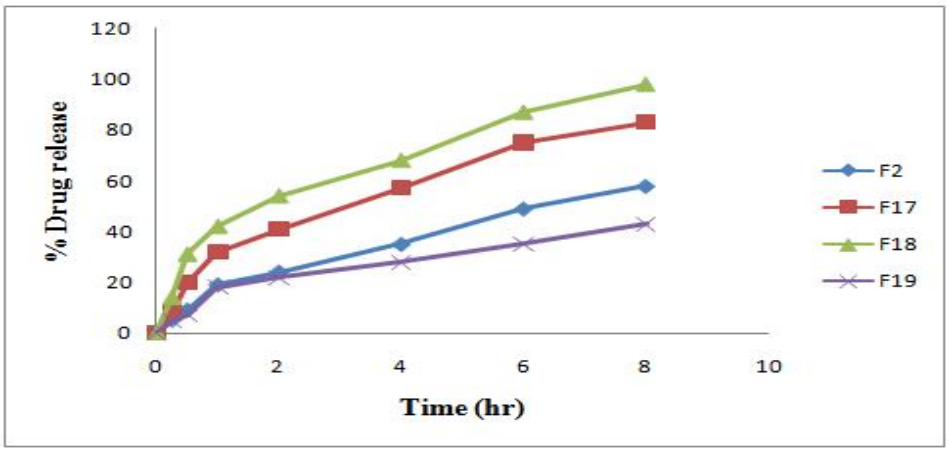

Figure 5: Effect of the type of matrix-forming polymer on verapamil HCl release in 0.1 N HCl from floating matrix tablets (initial radius 6 mm, 360 mg tablet weight/120 mg drug, 90 mg foam powder, 150 mg polymer; compositions in Table1, formulation Nos. 2, 17, 18 and 19).

v. Effect of the type and amount of filler

The effect of adding water-soluble (lactose) and water insoluble [microcrystalline cellulose (MCC) and dibasic calcium phosphate (Emcompress)] fillers to low density matrix tablets containing verapamil HCl, polypropylene foam powder, and HPMC K15M on the resulting drug release kinetics is shown in Figure 6A. Clearly, the release rate increased when adding the fillers, however no differences were seen between the three different fillers at the investigated polymer/ filler ratio of 2:1. The slight increase in drug release can probably be explained by the decreas- ing relative HPMC amounts and, thus, the less tight hydrogel structures upon swelling. Thus, the physicochemical properties of the filler do not seem to affect the underlying drug release mechanisms and release rates in the present case. Vargas and Ghaly (1999) did also not observe any significant difference between lactose, MCC and Emcompress when used as filler in theophylline containing HPMC K4M-based matrix tablets with respect to the resulting drug release kinetics (containing up to 59% w/w filler).[16] Thus, HPMC is clearly the dominating com- pound controlling the release rate of the drug in the investigated low density matrix tablets.

When increasing the amount of added lactose, while simultaneously reducing the amount of the matrix-forming polymer (up to a ratio of 1:2 HPMC K15M/ lactose, keeping the total tablet weight constant), the drug release rate in 0.1 N HCl significantly increased (Figure 6B).

As discussed above, this can probably be attributed to the decreasing tightness of the swollen hydrogel.

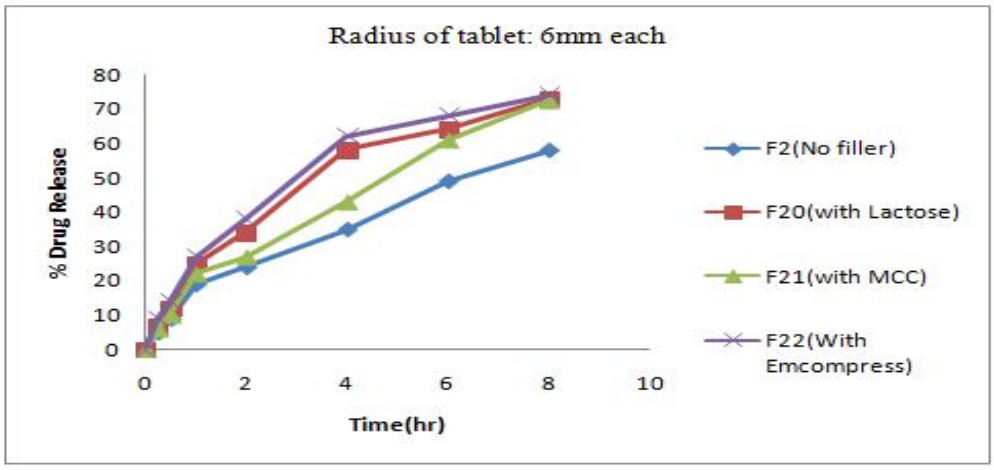

Figure 6A: Effect of adding different types of fillers (initial radius 6 mm, 360 mg tablet weight /120 mg drug, 90 mg foam powder, 100 mg HPMC K15M, 50 mg filler; compositions in Table1, formulation Nos. 2, 20, 21 and 22) .

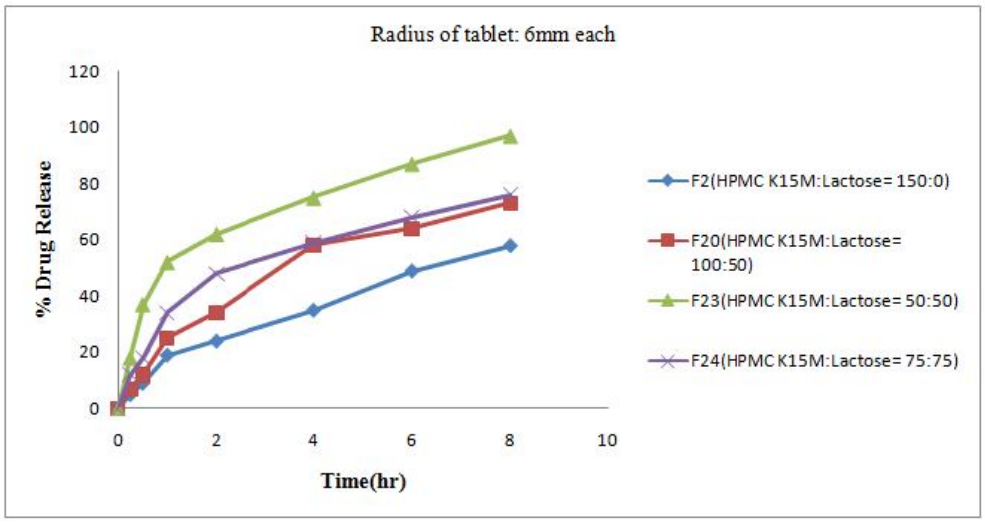

Figure 6B: Effect of the ''HPMC K15M/ lactose'' ratio (initial radius 6 mm, 360 mg tablet weight/120 mg drug, 90 mg foam powder, polymer/ lactose ratio given in the figure; compositions in Table1, formulation Nos. 2, 20, 23 and 24) on verapamil HCl release in 0.1 N HCl from floating matrix tablets.

vi. Effect of using blends of matrix-forming polymers

Instead of using only a single polymer, blends of different macromolecules can also serve as matrix formers. A broad range of drug release behaviors was obtained from matrix tablets

prepared with blends of HPMC K15M and various other hydrogel formers (Figure 7A). Gum arabic, gum guar, carrageenan and corn starch used as second hydrogel former led to a rather rapid drug release (more than 89% of the drug was released within the first 2 h). Thus, these systems cannot provide extended drug delivery over prolonged periods of time, probably due to rapid partial tablet disintegration (visual observation) and/or slower swelling of these polymers (resulting in a lack of contribution to hydrogel formation). However, with sodium alginate, NoveonAA1 and the different Carbopol types, sustained drug release was achieved, similar to systems based on only HPMC.

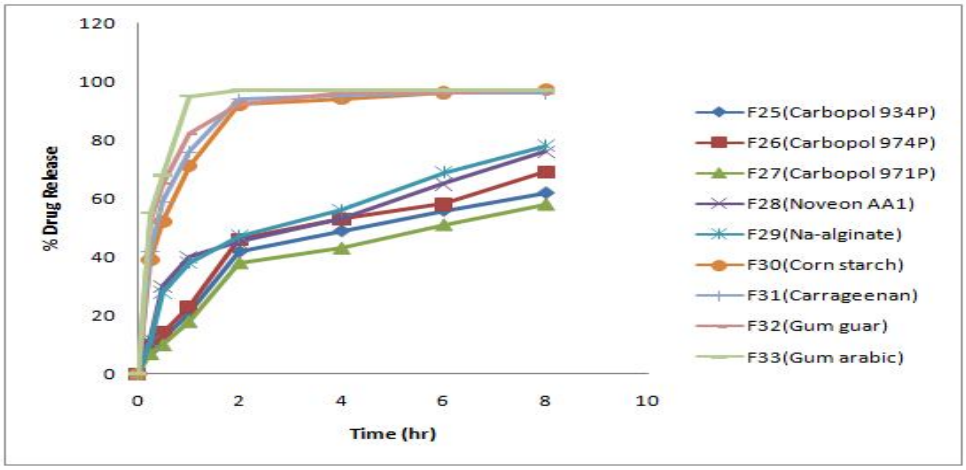

Figure 7A: Effect of the use of blends of matrix-forming polymers (initial radius 6 mm, 360 mg tablet weight/120 mg drug, 90 mg foam powder, 20 mg HPMC K15M, 30 mg second hydrogel former as given in the figure, 100 mg lactose; compositions in Table1, formulation Nos. 25 to 33), and the matrix-forming polymer blend ratio on verapamil HCl release in 0.1 N HCl from floating tablets.

The effect of varying the blend ratio on drug release for two hydrogel former combinations (HPMC K15M/ Carbopol 934P and HPMC K15M/sodium alginate) is illustrated in Fig. 7B and C. The effect of the blend ratio was much more pronounced in the case of HPMC K15M/ Carbopol (Figure 7B) mixtures compared to the HPMC K15M/sodium alginate blends (Figure 7C). As discussed above, drug release from tablets containing only Carbopol 934P was more sustained than from HPMC K15M-based systems (Figure 5). All blends of these polymers showed intermediate behavior. Interestingly, drug release from 4:1 and 3:2 blends (HPMC K15M/Carbopol) was very similar to the pure HPMC K15M systems. Thus, HPMC K15M is the dominant compound, controlling drug release in these blends. However, if more Carbopol than HPMC is present in the system, this domination no longer holds. Intermediate

release between the two pure polymers is obtained in the case of 2:3 blends. Interestingly, the release of verapamil HCl from pure HPMC K15M and pure sodium alginate-based systems was faster than from tablets containing the respective polymer blends (Figure 7C). This might be explained by polymer–polymer interactions between HPMC K15M and sodium alginate.

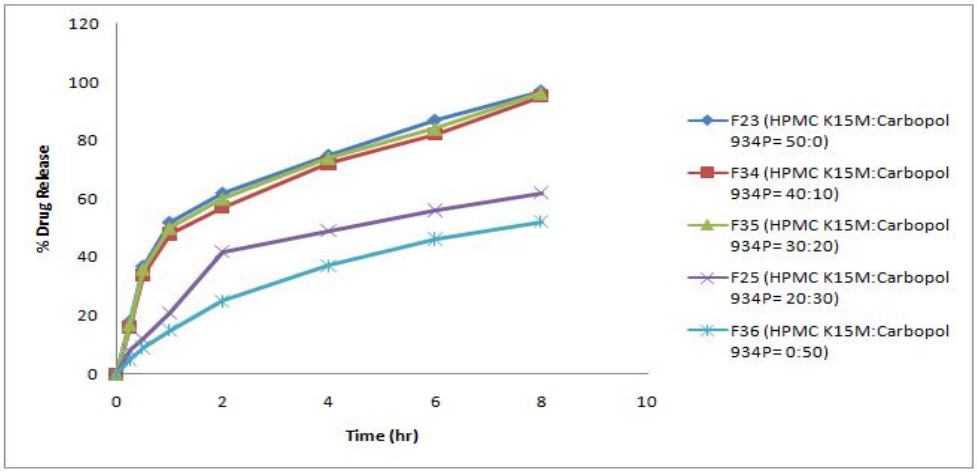

Figure 7B: Effect of blends of HPMC K15M and Carbopol 934P.

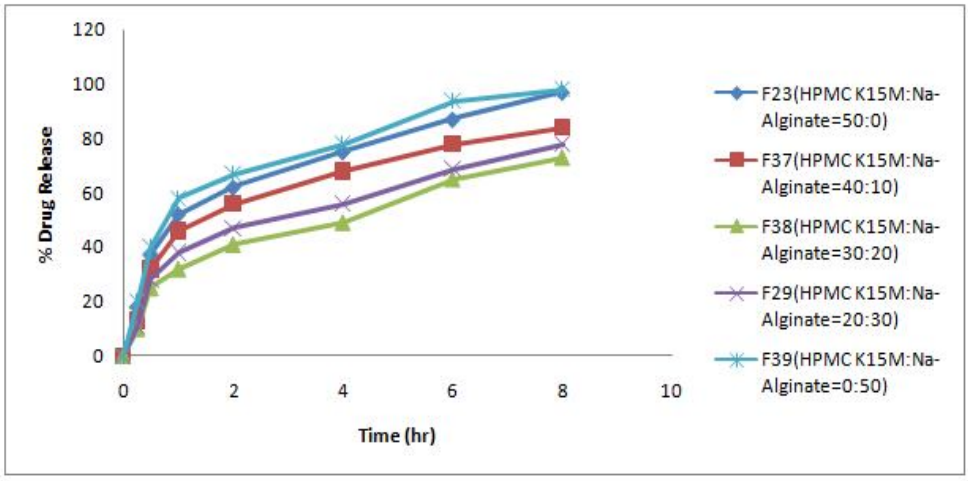

Figure 7C: Effect of blends of HPMC K15M and sodium alginate (initial radius 6 mm, 360 mg tablet weight/120 mg drug, 90 mg foam powder, polymer /polymer blend ratio given in the figure, 100 mg lactose; compositions in Table1, formulation Nos. 23, 25, 29, 34 to 39).

CONCLUSIONS

A single unit, floating drug delivery system has been developed, which is based on low density foam powder and matrix-forming polymer(s). Its in vitro floating performance and the ability to control drug release over prolonged periods of time have been demonstrated.

The drug release patterns can effectively be adjusted by varying simple formulation parameters, such as the matrix-forming polymer / foam powder ratio, initial drug loading, tablet height and diameter, type of matrix-forming polymer, addition of water-soluble and water-insoluble fillers, and the use of polymer blends. Thus, desired release profiles adapted to the pharmacokinetic /pharmacodynamic properties of the incorporated drug can easily be provided.

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REFERENCE

1. Ichikawa M, Watanake S, Yake YM. A new multiple unit oral floating dosage systems: Preparation and *in vitro* evaluation of floating and sustained release characteristics. J Pharm Sci. 1991; 80: 1062-6.
2. Yeole PG, Khan S, Shah K. Floating drug delivery system: Need and development. Int J Pharm Sci. 2005;67: 265-72.
3. Rahman Z, Ali M, Khar RK. Design and evaluation of bilayer floating tablets of captopril. Acta Pharma. 2006;56:49-57.
4. Hiremath SN, Farhat F, Swamy PV, Ramanamurthy KN. Design and *in vitro* evaluation of hydrodynamically balanced system of famotidine. Ind Drug. 2007; 44: 767-71.
5. Moes A.J. Gastroretentive dosage forms. Crit. Rev. Ther. Drug Carrier Syst. 1993; 10: 143–195.
6. Deshpande A.A., Rhodes, C.T., Shah, N.H., Malick, A.W. Controlled-release drug delivery systems for prolonged gastric residence: an overview. Drug Dev. Ind. Pharm. 1996; 22: 531–539.
7. Rouge N., Buri, P., Doelker, E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int. J. Pharm. 1996; 136: 117–139.
8. Hwang S.J., Park, H., Park, K. Gastric retentive drug-delivery systems. Crit. Rev. Ther. Drug Carrier Syst. 1998; 15: 243–284.
9. Singh B.N., Kim, K.H. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Release, 2000; 63: 235–259.

10. Bodmeier R., Paeratakul, O. Process and formulation variables affecting the drug release from chlorpheniramine maleate-loaded beads coated with commercial and self-prepared aqueous ethyl cellulose pseudolatexes. Int. J. Pharm, 1991; 70: 59–68.
11. Bodmeier R., Guo, X., Sarabia, R.E., Skultety, P.F. The influence of buffer species and strength on diltiazem HCl release from beads coated with the aqueous cationic polymer dispersions, Eudragit RS, RL 30D. Pharm. Res. 1996; 13: 52–56.
12. Streubel A., Siepmann, J., Dashevsky, A., Bodmeier, R. pH- independent release of a weakly basic drug from water-insoluble and soluble matrix tablets. J. Control. Release. 2000; 67: 101–110.
13. Bodmeier R., Chen, H. Evaluation of biodegradable poly(lactide) pellets prepared by direct compression. J. Pharm. Sci. 1989; 78: 819–822.
14. The Merck Index, Merck Research Laboratories, 12th ed. Merck and Co., Inc.1996
15. http://www.scbt.com/datasheet-204726-diltiazem.html
16. Vargas C. L. , E. S. Ghaly. Kinetic release of theophylline from hydrophilic swellable matrices, Drug Dev. Ind. Pharm. 1999; 25: 1045-1050.