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Formulation and Evaluation of Glipizide Floating-Bioadhesive Tablets

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ABSTRACT

The purpose of this study was formulation and in vitro evaluation of floating-bioadhesive tablets to lengthen the stay of glipizide in its absorption area. Effervescent tablets were made using chitosan (CH), hydroxypropyl methylcellulose (HPMC), carbopolP934 (CP), polymethacrylic acid (PMA), citric acid, and sodium bicarbonate. Tablets with 5% effervescent base had longer lag time than 10%. The type of polymer had no significant effect on the floating lag time. All tablets floated atop the medium for 23-24 hr. Increasing carbopolP934 caused higher bioadhesion than chitosan ($p < 0.05$). All formulations showed a Higuchi, non-Fickian release mechanism. Tablets with 10% effervescent base, 80% CH/20% HPMC, or 80% CP/20% PMA seemed desirable.

Key words: Glipizide, Floating-bioadhesive, Tablets, non-Fickian release

INTRODUCTION

The earliest studies in the field of modified drug delivery date back to the 1950s. Since then, a large number of drug products, mainly in the form of tablet and capsule with controlled release characteristics, have been introduced. Das and Das predicted a minimum growth of 9% per year for this market through 2003 (Das and Das, 2003). This incredible growth can be attributed to several advantages that these products offer, including improved patient compliance, better therapeutic efficiency, potential for cost saving and patentability, and opportunity for extending the product life-cycle.

Oral sustained-release technology provides oral delivery for 24 h; however, in substances that cannot be well absorbed throughout the whole gastrointestinal tract, it may be disadvantageous (Baumgartner et al. 2000). Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for the drugs with narrow absorption windows, stability problems in the intestinal or colonic environments, locally acting in the stomach, and poor solubility in the intestine (Streubel, Siepmann, and Bodmeier 2003). Recent approaches to increase the gastric residence time of drug delivery systems include bioadhesive devices (Alvisi et al. 1996; Ponchel and Irache 1998; Patel and Chavda 2009), swelling devices that increase their size (Urquhart and Theeuwes 1984; Mamajek 1980), low density devices (Streubel et al. 2003; and Raval et al. 2007), floating systems (Deshpande et al. 1997 and Dave et al. 2004), high density systems (Bechgaard and Ladefoged 1978; Davis et al. 1986), magnetic systems, unfoldable and expandable systems, magnetic systems, superporous, biodegradable hydrogel systems

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(Singh et al. 2000) and microparticulate systems (Patel and Chavda 2009).

The otherwise-excellent concept of floating system suffers from a disadvantage that it is effective only when the fluid level in the stomach is sufficiently high. However, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded (Chueh, Zia, and Rhodes 1995). This serious limitation can be overcome by using bioadhesive polymers to enable it to adhere to the mucous lining of the stomach wall (Chitnis, Malshe, and Lalla 1991). Floating and bioadhesive drug delivery systems offer the advantages of increased contact time with stomach mucusa, more effective absorption and bioavailability of drugs with absorption windows near proximal intestine and stomach, and low dosing frequencies (Lehr CM et al. 1992; Chueh et al.1995 and Rao et al. 1997).

The various buoyant preparations include microballoons, microspheres, granules, powders, gel, capsules, tablets, and laminated films (Singh et al. 2000). Based on the mechanism of buoyancy, two distinctly different technologies, i.e., noneffervescent and effervescent systems have been utilized in the development of floating systems: 1. Noneffervescent systems that use commonly gel-forming or highly swellable cellulose-type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene (Singh et al. 2000). 2. Effervescent systems that utilize the matrices prepared with swellable polymers such as HPMC or chitosan and effervescent compounds, e.g., sodium bicarbonate and citric or tartaric acid (Rubinstein and Friend 1994) or matrices containing chambers of liquid that gasify at body temperature (Ritschel 1991). Matrix tablets based on hydroxypropyl methylcellulose (HPMC K4M) have been developed by Li et al. (2000, 2003). Natural gums in combination with HPMC also have been evaluated for gel-forming properties (Dave et al. 2004). Microparticulate systems using natural polymers have been evaluated for stomach specific drug delivery of glipizide (Patel et al. 2005). Different mass transport processes may occur during the drug release from the polymer-based matrix tablets, including water imbibition into the system, polymer swelling, drug dissolution, drug diffusion out of tablet, and polymer dissolution (Siepmann et al. 2002).

Glipizide is a second-generation sulfonylurea that can acutely lower the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat type II diabetes (non-insulin-dependent diabetes mellitus). Its short biological half-life (3.4 ± 0.7 h) necessitates that it be administered in two or three doses of 2.5 to 10 mg per day. (Foster and Plosker, 2000). Glipizide is available in a Gastrointestinal Therapeutic System (GITS) extended-release formulation. Glipizide GITS provides more stable plasma drug concentrations than the immediate-release formulation and the once-daily regimen may optimize patient compliance. In patients with type II diabetes mellitus, glipizide GITS is at least as effective as the immediate-release formulation of glipizide in providing glycaemic control, and may have a greater effect on fasting plasma glucose levels. Any therapeutic advantage over other antidiabetic agents remains to be established, but in a preliminary report (n = 40) glipizide GITS provided better glycaemic control and produced less fasting insulinaemia than glibenclamide (glyburide) (Foster and Plosker, 2000). Menger et al (2002) compared the pharmacokinetic and short-term pharmacodynamic profile of extended-release glipizide (GITS) given with that of immediate-release glipizide in patients with type II diabetes mellitus. At steady state, the mean Cmax after immediate-release glipizide was significantly greater than after glipizide GITS, and the tmax was considerably shorter. Although the mean Cmin with glipizide GITS was about 80% higher than with immediate-release glipizide, the mean AUC 0-24 was significantly lower. Despite the lower plasma concentrations with glipizide GITS in this short-term study, the two formulations had similar effects on serum concentrations of glucose, insulin, and C-peptide. The absence of a pronounced peak plasma concentration with the GITS formulation might confer advantages in terms of maintaining the clinical effectiveness and reducing the potential to cause adverse effects. Thus, the development of controlled/extended release dosage forms of glipizide would clearly be advantageous. Researchers have formulated oral controlled-release products of glipizide by various techniques (Thombre el al. 1999, Chowdary et al. 2003 and Patel et al. 2005).

The hypothesis for this study was that if glipizide could be delivered in a controlled manner to the duodenum at a rate that did not exceed the

maximum rate of its absorption, then the oral bioavailability of glipizide could be improved. Based on this hypothesis, the gastric floating and bioadhesive tablets were designed in such a way that they should be retained in the stomach for a prolonged period of time, thus maximizing the exposure of this drug to its absorption site.

MATERIALS AND METHODS

Glipizide was obtained as gift sample from USV Ltd (Daman, India). Chitosan (degree of deacetylation of 85%; intrinsic viscosity, 1390 mL/g in 0.30 M acetic acid/0.2 M sodium acetate solution; and viscometric molecular weight, 4.08×10^5 Da) was obtained as gift sample from the Central Institute of Fisheries Technology (Cochin, India), hydroxypropyl methylcellulose (HPMC K4M), (Zydus Cadila, Ahmedabad, India), carbopolP934 (Noveon, Mumbai, India), polymethacrylic acid (PMA) (Zydus Cadila, Ahmedabad, India), citric acid (Merck, Germany), and sodium bicarbonate (Merck, Germany) were used.

Preparation of Bioadhesive and Floating Tablets

In the tablet formulation, HPMC/CH or CP934/PMA were used as bioadhesive agents. These polymers produce gel-forming matrices and, in contact with gastric fluid, possess sufficient structure to form a gel layer and achieve an overall specific gravity lower than that of gastric fluid. Citric acid and sodium bicarbonate were used as effervescent base to generate the carbon dioxide and to enhance the buoyancy of the tablets. All powders, except magnesium stearate were sieved through mesh size 20. The components of the formulation were mixed for 20 min in a cubic mixer. Magnesium stearate (60-mesh sieved) was added into powder blend as a lubricant and mixed for an additional 3 min the before compaction process. Then 200 mg tablets containing 10 mg glipizide were prepared by a lab press (Cadmach Csi 670, India) under a pressure of 50 kg/cm^2 using two flat face punches with a 7.9-mm diameter. The tablet formulations are shown in Table 1. Evaluation of the tablets was also done for the weight variation test and hardness as given in Table 2.

Table 1 - Ingredients in mg of floating-bioadhesive tablets of glipizide.

Formulation code	Sodium bicarbonate	Citric acid	Hydroxypropyl methylcellulose	Chitosan	Polymethacrylic acid	CarbopolP934
JE5H100	9.5	9.5	169	0	-	-
JE5H80CH20	9.5	9.5	132	37	-	-
JE5H60CH40	9.5	9.5	113	56	-	-
JE5H40CH60	9.5	9.5	56	113	-	-
JE5H20CH80	9.5	9.5	37	132	-	-
JE5CH100	9.5	9.5	0	169	-	-
JE10H100	18.5	18.5	151	0	-	-
JE10H80CH20	18.5	18.5	121	30	-	-
JE10H60CH40	18.5	18.5	90	61	-	-
JE10H40CH60	18.5	18.5	61	90	-	-
JE10H20CH80	18.5	18.5	30	121	-	-
JE10CH100	18.5	18.5	0	151	-	-
JE10P100	18.5	18.5	-	-	151	0
JE10P80CP20	18.5	18.5	-	-	121	30
JE10P60CP40	18.5	18.5	-	-	90	61
JE10P40CP60	18.5	18.5	-	-	61	90
JE10P20CP80	18.5	18.5	-	-	30	121
JE10CP100	18.5	18.5	-	-	0	151

All tablets contain 10 mg glipizide and 2 mg magnesium stearate as lubricant

Table 2 - Physical properties of floating-bioadhesive tablets of glipizide (n=3).

Formulation code	Density (g/cm^3)	Hardness (kg/cm^2)	Wt. variation test (%)	Floating lag-time (sec)	Floating duration (hr)
JE5H100	0.982 ± 0.016	5.2 ± 0.3	Av. ± 1.75	105.0 ± 5.4	23.5 ± 1.0
JE5H80CH20	1.078 ± 0.023	5.4 ± 0.2	Av. ± 1.50	105.0 ± 8.2	24.0 ± 1.5
JE5H60CH40	1.011 ± 0.043	4.8 ± 0.1	Av. ± 1.25	75.4 ± 3.7	23.5 ± 1.5
JE5H40CH60	1.103 ± 0.076	4.9 ± 0.1	Av. ± 1.00	87.2 ± 11.4	24.0 ± 1.5
JE5H20CH80	0.992 ± 0.026	4.3 ± 0.2	Av. ± 1.25	84.4 ± 12.4	23.5 ± 2.0
JE5CH100	1.102 ± 0.065	4.2 ± 0.1	Av. ± 1.50	89.5 ± 4.6	24.5 ± 2.5
JE10H100	0.970 ± 0.058	5.1 ± 0.3	Av. ± 1.20	47.8 ± 5.4	24.0 ± 2.0
JE10H80CH20	1.067 ± 0.098	4.8 ± 0.2	Av. ± 1.05	49.2 ± 10.0	23.5 ± 2.5
JE10H60CH40	1.072 ± 0.097	4.4 ± 0.1	Av. ± 1.75	54.0 ± 11.1	23.5 ± 2.0
JE10H40CH60	1.042 ± 0.145	4.2 ± 0.1	Av. ± 1.25	53.1 ± 9.6	24.0 ± 2.5
JE10H20CH80	1.045 ± 0.078	4.1 ± 0.2	Av. ± 1.50	45.9 ± 3.2	23.0 ± 1.0
JE10CH100	1.045 ± 0.098	4.2 ± 0.1	Av. ± 1.00	52.5 ± 4.4	23.0 ± 1.0
JE10P100	1.013 ± 0.058	4.0 ± 0.2	Av. ± 1.25	51.7± 9.0	23.0 ± 3.0
JE10P80CP20	1.065 ± 0.065	4.2 ± 0.1	Av. ± 1.05	51.0 ± 8.9	24.5 ± 2.5
JE10P60CP40	1.045 ± 0.043	4.4 ± 0.2	Av. ± 1.40	53.2 ± 11.2	23.5 ± 2.5
JE10P40CP60	0.995 ± 0.057	4.8 ± 0.1	Av. ± 1.50	54.0 ± 8.6	23.0 ± 2.0
JE10P20CP80	0.976 ± 0.104	5.0 ± 0.2	Av. ± 1.25	45.8 ± 4.6	23.5 ± 3.0
JE10CP100	1.042 ± 0.097	5.0 ± 0.2	Av. ± 1.50	52.0 ± 10.3	24.0 ± 1.0

Floating Behavior of Tablets

The in vitro floating behavior of the tablets was studied in 500 ml preheated 0.1NHCl (pH 1.2, 37°C, no enzyme) and stirred at 50 rpm with a paddle (USP paddle method). 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. The results of the in vitro buoyancy study of batch JE10H20CH80 are shown in Fig. 1.

Measurement of Bioadhesive Strength of the Tablets

The bioadhesive strength of the prepared tablets was measured on a modified physical balance (Gupta et al. 1992 and Ali et al. 2002). Albino rat stomach was used as the membrane and isotonic phosphate buffer (IPB), pH 6.6, was used as the moistening fluid. The stomach membrane was excised by removing the underlying tissues. It was washed thoroughly with IPB (pH6.6) and then tied over the protrusion in the Teflon block using a thread. The block was lowered into the glass container filled with IPB (pH 6.6) at 37±2 °C such that the buffer just touched the sides of the stomach membrane. The two sides of the balance were made equal before the study by keeping 5.0 g weight on the right pan. The glass container was kept below the left hand side of the balance. The tablet was stuck onto the lower side of the hanging Teflon cylinder using either a little moisture or a double sided tape. The surface of the stomach membrane was blotted with a Whatman filter paper and 25 µl of IPB (pH 6.6) was added to the stomach surface. This was done in order to obtain reproducible results. The 5.0 g weight from the right pan was removed. This lowered the Teflon cylinder along the patch over the stomach membrane with a weight of 5.0 g. This was kept undisturbed for two minutes. Then the weights on the right hand side were slowly added in increments of 0.5 g till the tablet just separated from the stomach membrane surface. The excess weight on the right pan, total weight minus 5.0 g was taken as a measure of the bioadhesive strength. The equipment was located in an air-conditioned room at 22°C and 60% relative humidity.

Density Measurements

The apparent densities of the tablets were calculated from their volumes and masses in triplicate. The volumes V of the flat face plain tablets were calculated from their heights h and radius r (both determined with a micrometer gauge) using the mathematical equation for a flat face plain ($V = \pi \times r^2 \times h$). The tablets with ~1 g/cm^3 density or less were chosen for further studies (Chueh et al. 1995).

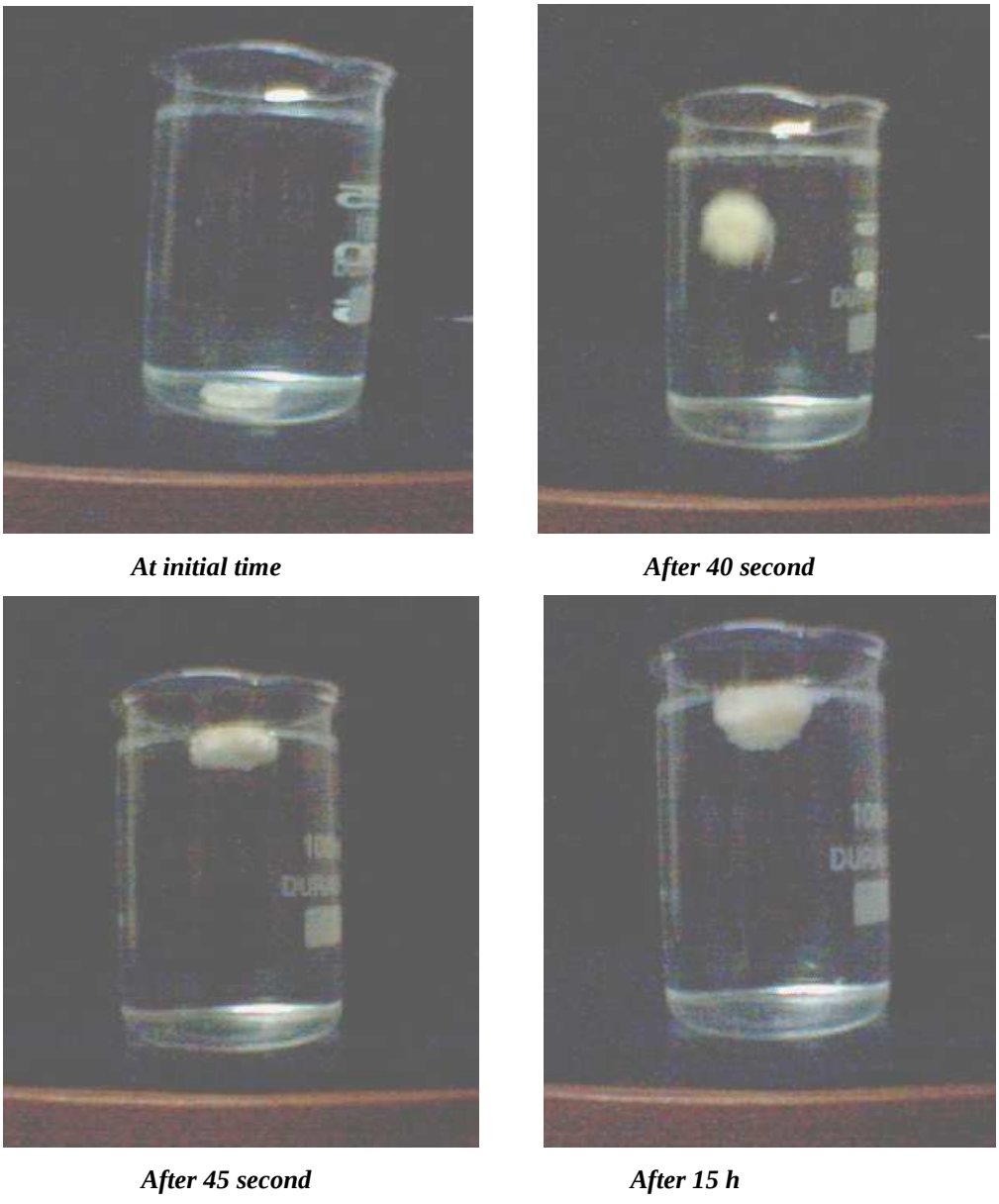

Figure 1- In vitro buoyancy studies of batch JE10H20CH80

Drug Release Study

The drug-release study was carried out using a USP XXIV type-2 (wire helix) apparatus (Electrolab, TDT-06T, India) at 37 ± 0.5°C and at 50 rpm using 250 ml of phosphate buffer (pH 7.4) as a dissolution medium (n = 5) as per the USP XXVI dissolution test prescribed for glipizide extended-release tablets (USP, 2003). Floating-bioadhesive tablets of glipizide (10 mg) were used for the test. A 5-ml sample solution was withdrawn at predetermined time intervals, filtered through a 0.45-micrometer membrane filter, diluted suitably, and analyzed spectrophotometrically. An equal amount of fresh dissolution medium was replaced immediately, following the withdrawal of the test sample. The percentage of drug dissolved at different time intervals was calculated using the Lambert-Beer's equation ($y = 0.1619x + 0.0139$, $R2 = 0.993$).

Data Fitting

Dissolution efficiency (DE) (Banakar 1992) after 8 h of release test was used to compare the results of dissolution tests of different formulations:

$$DE_8\% = \frac{\int_0^t y\,dt}{y_{100}t} \times 100 \quad [1]$$

The other dissolution parameter used for comparing the different formulations was mean dissolution time or MDT that was calculated from the amount of drug released to the total cumulative drug. MDT is a measure of the rate of the dissolution process: the higher the MDT, the slower the release rate. The following equation was used to calculate the MDT from the mean dissolution data:

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \quad [2]$$

Where i is the dissolution sample number, n is the number of dissolution sample time, tmid is the time at the midpoint between i and i − 1, and ΔM is the additional amount of drug dissolved between i and i − 1 (Gohel and Panchal 2002).

RESULTS

Table 2 shows the results of floating time and density of tablets. Data showed that increasing the effervescent base of tablets from 5 to 10% significantly lowered the lag time of floating from about 105 sec to 45 sec. All the batches showed good in vitro buoyancy. The results of the in vitro buoyancy study of batch JE10H20CH80 are shown in Fig. 1. The figure clearly indicated the floating lag time (45 seconds) of the glipizide tablets and the floating and swelling tendency of the formulation. The tablet swelled radially and axially. The figure also indicates that the tablet remained buoyant for 15 h, but the tablet actually floated throughout the entire study. The in vitro buoyancy study was also conducted at an elevated pH condition (~4.5). The floating tendency remained unaltered at higher pH. In all the studied formulations, the density was ~1 or less than 1 g/cm^3.

The results of bioadhesion studies are shown in Fig. 2. The tablets with 5 or 10% effervescent base in a matrix of HPMC/CH and 10% effervescent base in matrix of CP/PMA were compared for the bioadhesion in this figure. Figs. 3 and 4 show the effect of different ratios of HPMC and CH in tablets with two different percentages of effervescent base on drug release profiles. Fig. 5 compares the effect of gas generating agent concentration on drug release rate of HPMC/CH tablets. This figure showed that the tablets with higher gas-forming agent facilitated drug release. Fig. 6 compares the different ratios of CP/PMA from a release characteristic point of view. In all the formulations curve-fitting method was used to determine drug release kinetics (Table 3).

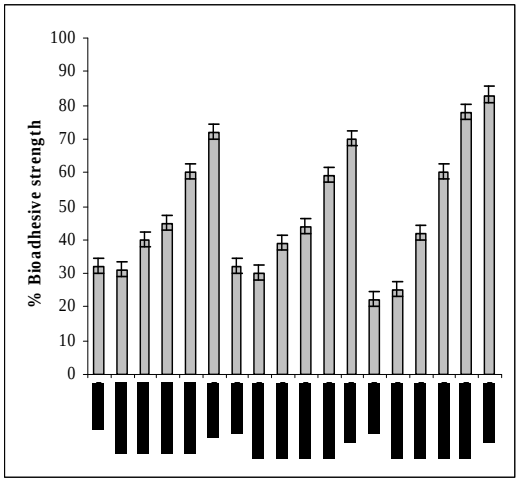

Figure 2 - Bioadhesive strength of different floating-bioadhesive tablets of glipizide.

Table 3 - Results of mean dissolution time (MDT), dissolution efficiency after 8 hr ($DE_{8\%}$), time required for release 50% of drug ($T_{50\%}$), and diffusion exponent (n).

Formulation code	n	MDT (hr)	$DE_{8\%}$	$T_{50\%}$ (hr)
JE5H100	0.77	3.52	59.24	8.54
JE5H80CH20	0.87	3.41	55.23	8.65
JE5H60CH40	0.71	3.22	62.65	6.54
JE5H40CH60	0.50	3.21	67.75	5.78
JE5H20CH80	0.51	3.22	68.93	4.76
JE5CH100	0.53	2.81	75.34	3.67
JE10H100	0.58	3.08	67.23	7.98
JE10H80CH20	0.47	2.52	76.23	8.14
JE10H60CH40	0.46	3.08	72.31	6.76
JE10H40CH60	0.50	2.86	78.97	6.47
JE10H20CH80	0.52	3.42	82.12	7.83
JE10CH100	0.52	2.52	84.22	5.84
JE10P100	0.69	3.57	65.74	26.54
JE10P80CP20	0.70	2.12	98.25	12.56
JE10P60CP40	0.68	2.25	96.57	5.09
JE10P40CP60	0.67	2.32	94.75	2.37
JE10P20CP80	0.57	2.34	86.98	2.45
JE10CP100	0.47	2.52	86.40	3.12

Dissolution results were analyzed using the semiempirical equation:

$$M_t/M_\infty = Kt^n \qquad [3]$$

where $Mt/M\infty$ represents the fraction of drug released at time *t, K* is the diffusional constant characteristic of the drug/polymer system, *t* is the release time, and *n* is an exponent characterizing the mechanism of release of the drugs (Korsmeyer and Peppas 1983). Table 4 summarizes the range of values of the diffusional exponent *n* and the corresponding release mechanism. The *n* values were in the range of 0.45-0.85, representing a non-Fickian or anomalous transport. This table also represents the release parameters i.e., MDT, $DE_{8\%}$, and $t_{50\%}$.

DISCUSSION

Studies have shown that some polymers such as carbopolP934, polymethacrylic acid, chitosan, and hydroxypropyl methylcellulose are among the floating polymers that show bioadhesive properties more than other polymers and have been used in the production of bioadhesive tablets. As these polymers are well hydrated and can adhere to the mucosal membranes, especially if a combination of them is used, their properties are improved (Ahuja, et al.1997). Bioadhesive systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner (Chickering and Mathiowitz 1999). The approach involves the use of bioadhesive polymers that can adhere to the epithelial surface of the gastrointestinal tract. The proposed mechanism of bioadhesion is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary (Wilson and Washington 1989).

Floating dosage forms are meant to remain buoyant on the gastric fluid when the stomach is full after a meal; however, as the stomach empties and the tablet is at the pylorus the buoyancy of the dosage form may be impeded (Muller-Lissnir and Blum 1981). It then becomes increasingly likely that the dosage form will pass through the pylorus into the small intestine. Thus, the buoyant ability of a floating drug delivery system in the stomach could be limited to only 3-4 h. In a bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the stomach is full and semi liquid contents are churning around under the influence of peristaltic movement (Chueh et al. 1995).

A synergism between a bioadhesive system and a floating system also has been explored. Chitnis et al. (1991) synthesized a series of bioadhesive polymers that were cross-linked polymers of PMA

and CP. Floating tablets of isosorbide mononitrate were prepared and then coated with these polymers. The results showed good bioadhesion and low densities, indicating that the coat might confer buoyancy to these tablets. Patel et al (2005) prepared chitosan microspheres using cross-linked method. The results showed longer glycemic effect indicating good bioadhesion and low densities of these microspheres. The results of bioadhesion test (Fig. 2) showed that the bioadhesion was significantly higher in JE10CP100 tablets than other formulations ($p < 0.05$) and the following order is seen: JE10P100 <JE10H100 < JE10CH100 < JE10CP100.

Statistical analysis of bioadhesion between two groups of tablets containing HPMC/CH or CP/PMA showed that tablets with 80-100% and 60% of CP had higher bioadhesion than tablets containing the comparable amounts of CH ($p <0.05$). However, tablets with 20-40% CH, or those with pure HPMC, had high bioadhesion compared with tablets with similar amounts of CP or without CP ($p < 0.05$). Increasing the content of CP in a series prepared with CP/PMA increased the bioadhesion ($p < 0.05$). Chng et al. (1985) also reported that CP polymer adhered to the surface mucin of the epithelial cells and this caused a longer gastrointestinal transit time compared with PMA polymer. This was related to the charge of CP and neutral nature of PMA (Chng et al. 1985).

In the design of floating-bioadhesive glipizide tablets, the floatation was accomplished by incorporating gas-generating salts such as sodium bicarbonate and citric acid into a swellable matrix. The overall make-up of this particular matrix is of swellable polymers. As the dissolution medium was imbibed into the matrix, the interaction of fluid with effervescent base resulted in the formation and entrapment of carbon dioxide gas within the swollen gel, thus causing floatation as the matrix volume expanded and its density decreased. Results showed that the amount of gas-generating effervescent base had a significant effect on the lag time of the system buoyancy (Table 2). However, statistical analysis of duration of floating time in HPMC/CH and CP/PMA tablets with 10% effervescent base showed no change ($p < 0.05$) in duration of system buoyancy by changing the percentage or the type of polymer mixtures (Table 2). In other words, the amount of gas-generating agent was just effective on the buoyancy lag time, but as the gas was generated at the early times of contact of fluid medium with effervescent base, the swelling of polymers was controlling the duration of system buoyancy.

Yang et al. (1999) used a mixture of sodium bicarbonate and calcium carbonate to induce gas formation in intragastric floating tablets of tetracycline/metronidazole tablets. Li et al. (2002, 2003) used citric acid as gas-generating agent in floating capsules of calcium carbonate. A 1:1 mixture of potassium bicarbonate: monobasic potassium citrate as effervescent base of verapamil floating capsules has been reported by Gan-Lin and Wei-Hua (1998). Dave et al. (2004) used sodium bicarbonate and citric acid as gas-generating agent in floating tablets of ranitidine hydrochloride.

Drug release studies were made to determine whether the release of the drug was slow enough, i.e., which polymer percentage was enough to sustain the release of the drug for at least 8 h. As Figs. 3 and 4 showed, increasing the CH content of tablets significantly increased the percentage of drug released at comparable times ($p < 0.05$). This was because of rapid swelling and erosion of CH in contact with gastric fluid. Comparison of the tablets with the same formulations but different effervescent base concentrations (Fig. 6) showed faster release rate of drug and $DE_{8\%}$ (Table 3) in the tablets with 10% of gas-generating agent than 5%. This was because of greater expansion of polymer matrix, better penetration of liquid medium into the tablet, and faster diffusion of drug. Table 3 showed that increasing CH content of tablets reduced MDT and $T_{50\%}$ while increasing the $DE_{8\%}$ ($p < 0.05$). Comparison of $T_{50\%}$ and MDT of tablets with the same ratio of HPMC/CH but different effervescent bases showed a decrease in these parameters in the tablets with 10% of gas-generating agent than 5% ($p < 0.05$) (Table 3).

In spite of more suitable sustained-release effect of the tablets with 5% effervescent base (Table 3), but as their long lag-time of buoyancy (Table 2), the tablets of JE10H60CH40 and JE10H40CH60 were chosen as optimum formulations (Fig. 4 and Table 3). However, as there were some difficulties in flow rate of powder in preparation of these tablets, formulation JE10H20CH80 also seemed optimum from floating lag time, bioadhesion, and sustained-release point of view. The tablets composed of a polymeric matrix build a gel layer around the tablet core on contact with gastric fluid, which controlled the drug release. Drug release from HPMC matrices is controlled by diffusion through the gel layer for water-soluble drugs or by

erosion of the outer polymer chains for poorly soluble drugs (Mitchell et al. 1993). The drug characteristics are as important as those of the gel. The size, shape, and ionization of the drug affect its diffusion through the gel layer (Peppas and Wright 1998).

Table 4 - Correlation coefficient of release data of floating-bioadhesive tablets of glipizide.

Formulation code	r^2		
	Zero-order	**First-order**	**Higuchi model**
JE5H100	0.9862	0.9863	0.9902
JE5H80CH20	0.9889	0.9891	0.9972
JE5H60CH40	0.9575	0.9765	0.9854
JE5H40CH60	0.9467	0.9790	0.9989
JE5H20CH80	0.9365	0.9786	0.9844
JE5CH100	0.9116	0.9702	0.9876
JE10H100	0.9566	0.9732	0.9878
JE10H80CH20	0.9109	0.9542	0.9809
JE10H60CH40	0.9045	0.9598	0.9877
JE10H40CH60	0.8154	0.9034	0.9531
JE10H20CH80	0.6589	0.8456	0.8794
JE10CH100	0.6439	0.8325	0.8567
JE10P100	0.9453	0.9532	0.9822
JE10P80CP20	0.9452	0.9598	0.9834
JE10P60CP40	0.8764	0.9412	0.9642
JE10P40CP60	0.8498	0.9501	0.9608
JE10P20CP80	0.8432	0.9523	0.9678
JE10CP100	0.6098	0.8145	0.8324

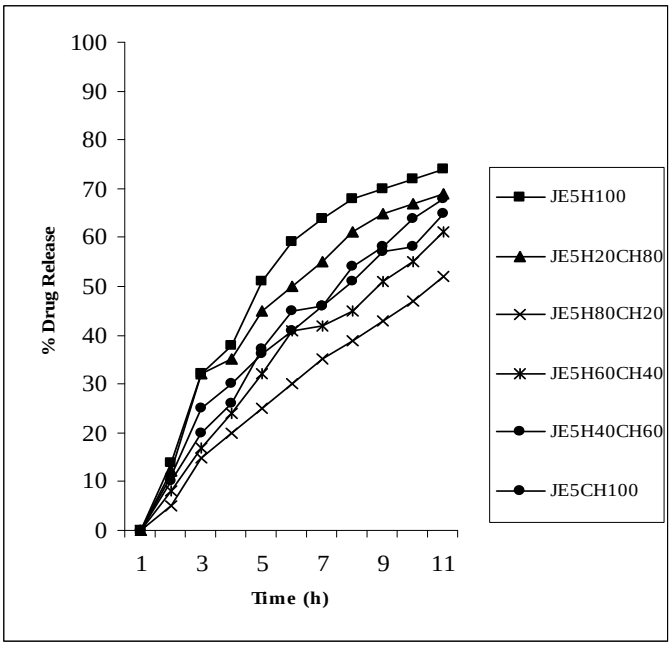

Figure 3 - Glipizide release profiles in phosphate buffer solution (pH 7.4) from floating-bioadhesive tablets containing 5 % effervescent base and HPMC/CH bland.

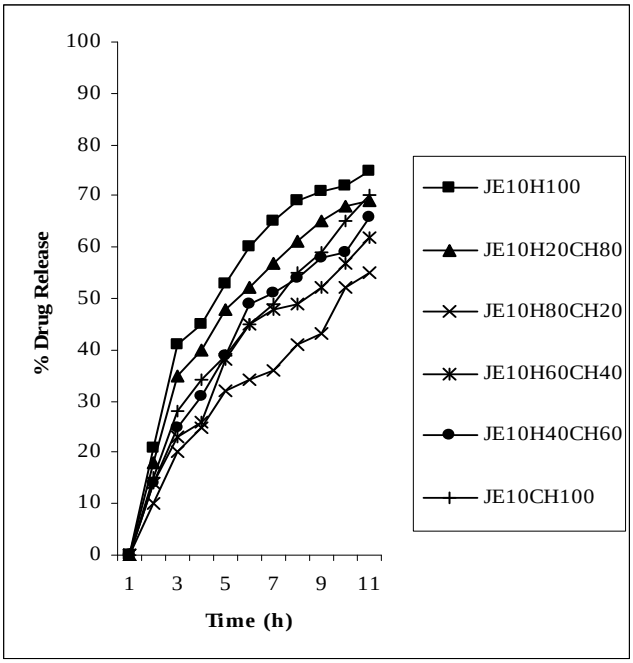

Figure 4 - Glipizide release profiles in phosphate buffer solution (pH 7.4) from floating-bioadhesive tablets containing 10 % effervescent base and HPMC/CH bland.

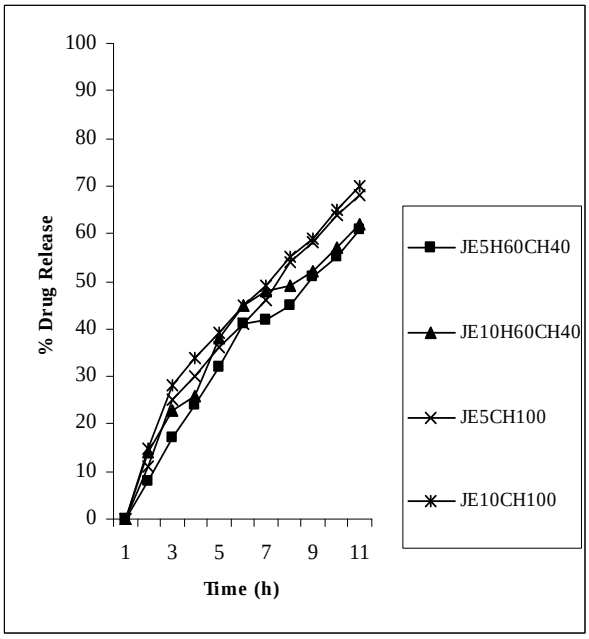

Figure 5 - Comparison between glipizide release profiles in phosphate buffer solution (pH 7.4) from floating-bioadhesive tablets containing 5 % or 10 % effervescent base and HPMC/CH bland.

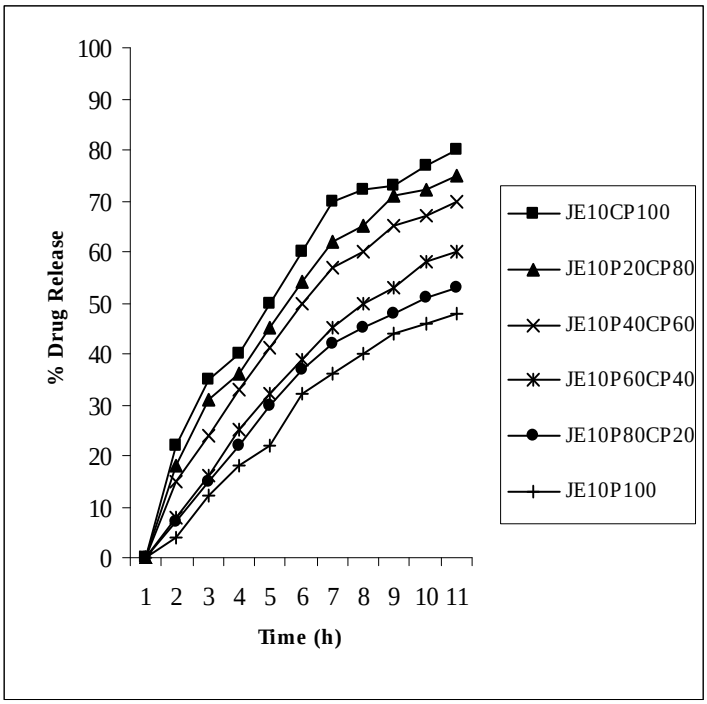

Figure 6 - Glipizide release profiles in phosphate buffer solution (pH 7.4) from floating-bioadhesive tablets containing 10 % effervescent base and CP/PMA bland.

In the tablets prepared from acrylate series, increasing the CP content, decreased the MDT and $T_{50\%}$ but increased the $DE_{8\%}$ significantly (p <0.05) (Table 3). Considering MDT and $DE_{8\%}$, tablets of JE10CP80P20, JE10CP60P40, and JE10CP40P60 seemed suitable for sustained-release of drug in the stomach (Table 3).

The study focused was the preparation of floating/bioadhesive tablets, thus the tablets of batches JE10H20CH80 and JE10P20CP80 were also evaluated in simulated gastric fluid USP (pH 1.2). The results indicated that no significant difference were observed between dissolution profiles at pH 7.8 and pH1.2 as the f_2 (similarity factor) value were 73.44 and 75.72, respectively.

Curve fitting method according to zero-order, first-order, or Higuchi model for analysis of drug release kinetics are shown in Table 4. In all cases, the Higuchi model was dominant and showed that the passage of glipizide, the water insoluble drug through the hydrated gel layer around the matrix tablet, was approximately dependent on the square root of time and could be described in the following form (Shah et al. 1993):

$$Q_t = Kt^{1/2} \quad [4]$$

where Qt is the amount of the released drug in time t, k is the kinetic constant, and t is time. To predict the mechanism of diffusional release, the following semiempirical equation of

$$M_t/M_\infty = Kt^n$$

was used to analyze the data of controlled-release of this water soluble drug from the studied polymer matrices (Peppas 1985; Yang and Fassihi 1997). In this equation, Mt is amount of the released drug at time t, $M\infty$ is the overall amount of the drug (whole dose), k is the constant incorporating structural and geometric characteristics of the controlled-release device, and n is the release exponent indicative of the drug release mechanism. For the tablets of a known geometry (in this case a slab) n = 0.5 means Fickian diffusion, 0.5 < n < 1.0 non-Fickian diffusion, and n = 1.0 Case II diffusion (Peppas 1985). Considering the n values calculated for the studied tablets (Table 3), in most cases, a non-Fickian mechanism was dominant. The drug diffusion through most types of polymeric systems is often best described by Fickian diffusion, but other processes in addition to diffusion are

important. In this case, the non- Fickian or anomalous diffusion shows a relaxation of the polymeric chains and influences the drug release. Release from the initially dry, hydrophilic glassy polymers that swell in contact of water and become rubbery show anomalous diffusion because of the rearrangement of macromolecular chains (Varshosaz et al. 2006). The thermodynamic state of the polymer and the penetrant concentration are responsible for the different types of the diffusion. A third class of diffusion is case II diffusion, which is a special case of non-Fickian diffusion (Peppas 1985; Mitchell et al. 1993). The results of the calculated *n* (Table 3) revealed a non-Fickian type of drug diffusion, which meant that the process of diffusion and relaxation ran at comparable rates.

CONCLUSIONS

This work described, a matrix floating-bioadhesive tablet incorporating an insoluble active substance. The most successful tablets with the least lag time of buoyancy were those prepared with 10% of effervescent base but changing the polymer type of mixture ratio did not change the duration of buoyancy. Tablets containing 20% of HPMC and 80% CH or 80% of CP and 20% of PMA were optimum from both the bioadhesion and prolonged drug release rate point of view.

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