Preparation and evaluation of a floating drug delivery system for Diltiazem HCl

Tavakoli N. [1*], Varshosaz J. [1], Dorkoosh[2] F., Rezazadeh[1] A.

[1] Faculty of pharmacy, Isfahan University of Medical Sciences, [2] Pharmaceutical R&D Department, Synthon BV, The Netherlands

Objectives: Approaches to increase the gastric residence time (GRT) include: floating drug delivery systems (FDDS), swelling-expanding forms, bio (muco) adhesive forms, modified shape and high density systems. Diltiazem HCl (DTZ), a model drug for this study, is a calcium antagonist used in the treatment of chronic heart diseases such as angina and hypertension. It has elimination half-life of 3.5 hours and hence is a suitable model candidate for gastro-retentive formulation. The major objectives of this study were to develop a single unit FDDS of DTZ and to study the effect of formulation and processing parameters on the floating and drug release of the system. **Methods:** DTZ matrix tablets (120 mg) containing HPMC (K4M, Colorcon, UK), Carbomer (934P, B.F. Goodrich, USA), Na CMC (Merck, Germany), Guar gum (Hercules, USA) and Xanthan gum (Arthur Branwell, UK) were prepared by direct compression method. All tablets contained an effervescent base consisting of sodium bicarbonate and citric acid. The tablets were evaluated for in vitro floating ability (floating lag time and duration of floating time), bioadhesiveness and drug release. Bioadhesion was measured by a method based on shearing tensile strength existing between tablets and a mucosal layer. The drug release studies were carried out using a dissolution apparatus (Erweka, Type DT700, Germany) basket method (100 rpm) in 900 ml of 0.1 N HCl buffer solution (pH = 1.2, 37°C). At appropriate time intervals, samples were withdrawn and assayed spectrophotometrically at 237.8 nm with suitable dilutions. **Results:** In vitro floating test showed that tablets containing 12% effervescent base had a floating lag time of 30-120 seconds. The duration of floating was 19-24 hours for all the formulations and the hardness of tablets had no significant effects on the floating time. The more carbomer content of the tablets, the more in the bioadhesive properties. Drug release data was fitted on both Higuchi and first order kinetic models. The mechanism of drug release showed a non Fickian (anomalous) behavior based on Korsmeyer-Peppas equation. **Conclusion:** We concluded that the proposed tablets with 12% effervescent base, 30% HPMC and 10% Na CMC showed good floating, bioadhesion and drug release properties in vitro and seems to be considered as FDDS for DTZ.
Key words: Diltiazem HCl, Floating drug delivery systems, Gastric residence time.

Corresponding Author: Dr Naser Tavakoli, Associate Professor, Faculty of pharmacy, Isfahan University of Medical Sciences, Tel: 0311-7922594; Fax: 0311-6680011; E-mail: tavakoli@pharm.mui.ac.ir

.( )

.

( )

. %

.( ) % .( )

( )

( )

–

. .( )

in vitro . :

)

(

.

.

: .( ) ( )

)

HPMC K4M) (

. ( ) .( )

(Arthur Branwell) Xanthan

) (Hercules) Guar) ( )

(BF Goodrich (

.( )

.(Merck) ( )

:

: .

( )

UV ( ) .

. /

USP

. (Japan Shimadzu) UV

: .( )

.( )

mg

$$\left| \log \frac{M_t}{M_\infty} = n \, Log \, kt \right|$$

M_∞ t M_t)

t .(

k

n $H_{30}C_{10}A$.

.( ) NaCMC % HPMC %

.( )

% DE MDT $T_{50\%}$

.

ANOVA (assay)

Duncan

P<0.05 . .

.

SPSS ( )

. XP Excel 2000 .( ) (Instron) Tensile strength

$\rho = M/V$

.( )

:

pH ( )

/ (pH = /) (rpm ± / C) /

$(r^2 = /)$.( )

.

/

.

.

± % /

.( )

)

(( )

. (mg %))

± / C / N

.( ) (rpm

(%CV) . (mg)

.( ) ( ) %

.

Korsmeyer-Peppas

( ) .

Na Bicarbonate	Citric acid	Xanthan	Guar	Carbopol	NaCMC	HPMC	Diltiazem HCl
( )							
							H30C10A
							H35C5A
							H30P10A
							X40A
							H30X10A
							H20X20A
							X20G20A
							G40A
							H20C20A
							H10C30A
							H25C15A
							H30C10A
							H30C10B

P = Carbopol 934   C =Na CMC   G = Guar gum   X =Xanthan gum

B =   A =   H =HPMC K4M

(n=)	(n=)	(n=)	(n=)	.
(g/cm3)	(%)	( )	(mg)	
/ ± /	/	/ ± /	/ ± /	H30C10A
/ ± /	/	/ ± /	/ ± /	H35C5A
/ ± /	/	/ ± /	/ ± /	H30P10A
/ ± /	/	/ ± /	/ ± /	X40A
/ ± /	/	/ ± /	/ ± /	H30X10A
/ ± /	/	/ ± /	± /	X20G20A
/ ± /	/	/ ± /	/ ± /	H20X20A
/ ± /	/	/ ± /	/ ± /	H30C10B
/ ± /	/	/ ± /	/ ± /	H30P10B
/ ± /	/	/ ± /	/ ± /	H30X10B

(n=)		(n=)	.
( )	( )	(mg)	
/ ± /	± /	/ ± /	H30C10A
/ ± /	± /	/ ± /	H35C5A
/ ± /	/ ±	/ ± /	H30P10A
± /	± /	/ ± /	X40A
±	± /	/ ± /	H30X10B
± /	± /	/ ± /	X20G20A
± /	± /	/ ± /	H20X20A
/ ± /	± /	/ ± /	H30C10B
±	± /	/ ± /	H30P10B
± /	±	/ ± /	H30X10B

٫٫

١١

pH   DE12% MDT T50%   .

/

$T_{50\%}$ (h) $\pm$ SD	DE_{12h}(%) $\pm$ SD	MDT(h) $\pm$ SD	
/ ± /	/ ± /	/ ± /	$H_{30}C_{10}A$
/ ± /	/ ± /	/ ± /	$H_{35}C_5A$
/ ± /	/ ± /	/ ± /	$H_{30}P_{10}A$
/ ± /	/ ± /	/ ± /	$X_{40}A$
/ ± /	/ ± /	/ ± /	$H_{30}X_{10}A$
/ ± /	/ ± /	/ ± /	$X_{20}G_{20}A$
/ ± /	/ ± /	/ ± /	$H_{20}X_{20}A$
/ ± /	/ ± /	/ ± /	$H_{30}C_{10}B$
/ ± /	/ ± /	/ ± /	$H_{30}P_{10}B$
/ ± /	/ ± /	/ ± /	$H_{30}X_{10}B$

DE_{12}%   MDT $T_{50\%}$.

(n =)

.

(n =)

.

(n =)

                  A   ) HPMC

(B   )   .

HPMC

www.SID.ir
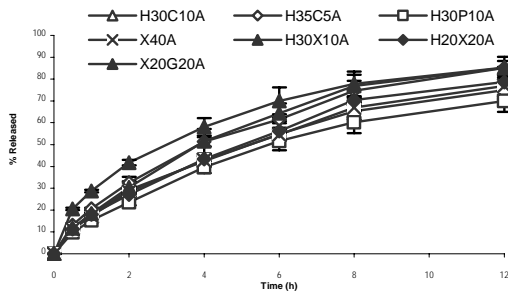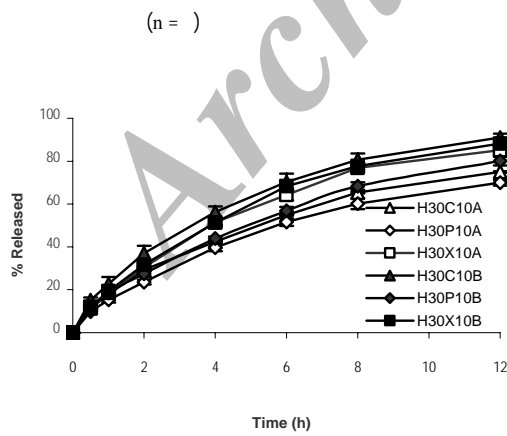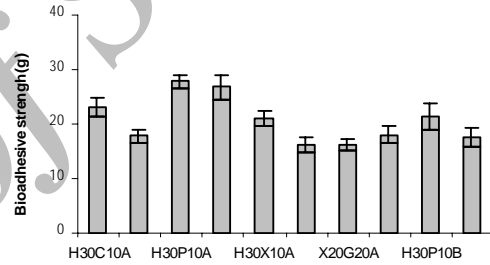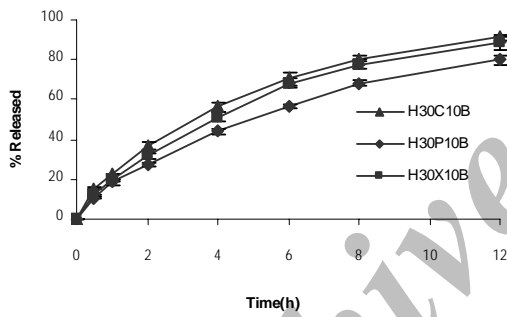
	n	
	n ≤ 0.45	
	0.5 ≤ n ≤ 0.8	
	0.8 ≤ n ≤ 1	(case II)
	n > 1	super-case II

.(   )

(P < 0.05)

:   .   ( )   ( )   ( )

.   ( )

.   )   ( )   GU

(

HPMC

:   .(   )   .

.   NaCMC   HPMC

Carbopol

.   %

(P<0.05)   HPMC   .

.

pH

HPMC   .( )

(H₃₀C₁₀A   )   .( )   K₄M

.

A   (/   )   pH

(   )

.( )

.

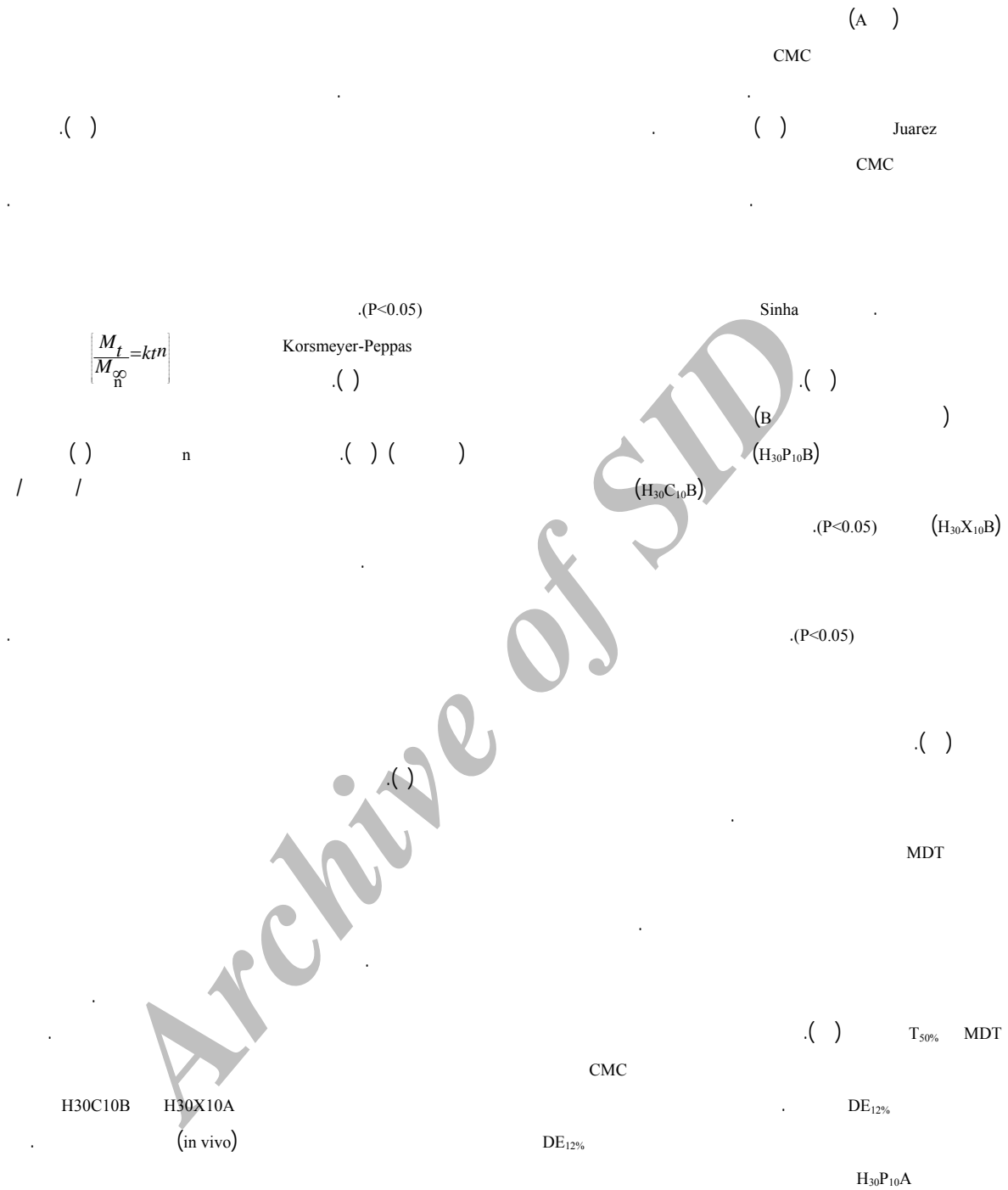B   .(P>0.05)   ( )   ( )

(   )

.   ( )

.(P<0.05)

HPMC

.( )

.(P>0.05)   ( )

.   HPMC

.

T50%   DE12%   MDT   .

$(A\ \ )$

CMC

.( )   .   ( )   Juarez

CMC

.   .

.(P<0.05)   Sinha   .

$$\left[\frac{M_t}{M_\infty}=kt^n\right]$$

Korsmeyer-Peppas

.( )   .( )

$(B\ \ \ \ \ \ \ \ \ \ \ \ )$

( )   n   .( ) (   ) $(H_{30}P_{10}B)$

/   / $(H_{30}C_{10}B)$

.   .(P<0.05) $(H_{30}X_{10}B)$

.   .(P<0.05)

.( )

.

MDT

.( )

.( ) $T_{50\%}$ MDT

CMC

H30C10B   H30X10A   . $DE_{12\%}$

. $(in\ vivo)$ $DE_{12\%}$

$H_{30}P_{10}A$

6- References:

1. Singh B.N., Kim K.H., Floating drug delivery system: an approach to controlled drug delivery via gastric retention, Journal of Controlled Release, 2000, 63: 235-259.

2. Baumgartner S, Krist J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. International Journal of Pharmaceutics, 2000, 195: 125-135.

3. Hilton A.K., Deasy P.B. In vitro and in vivo evaluation of an oral sustained-release floating

dosage form of amoxicillin trihydrate. International Journal of Pharmaceutics, 1992, 86: 79-88.

4. Sheth P.R., Tossounian J. The hydrodynamically balanced system (HBS[TM]): a novel drug delivery system for oral use. Drug Development and Industrial Pharmacy, 1984, 10: 313-339.

5. Rubinstein A., Friend D.R. Specific delivery to the gastrointestinal tract. In: Domb A.J., Polymeric site-specific pharmacotherapy. Chichester, NY, J. Wiley, 1994, 282-283.

6. Deshapande A.A., Rhodes C.T., Shah N.H., Malick A.W, Controlled-release drug delivery systems for prolonged gastric residence: an overview. Drug Development and Industrial Pharmacy, 1996, 22 (6): 531-539.

7. Longer M.A., Ch'ng HS, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery III: Oral delivery of chlorothiazide using a bioadhesive polymer. Journal of Pharmaceutical Sciences, 1985, 74: 406-411.

8. Alvisi V., Gasparetoo A., Dentale A., Heras H., Felletlispadazzi A., Ambrosi A. Bioavailability of a controlled release formulation of ursodeoxycholic acid in man. Drugs Experimental Clinical Research, 1996, 22: 23-29.

9. Sweetman SC, Martindale: The Complete Drug Reference. London, Pharmaceutical Press, 2005 (1), 900.

10. Whishead L., Fell J.T., Collett J.H, Development of a gastroretentive dosage form. European Journal of Pharmaceutical Sciences, 1996, 4(Supplement 1), S182

11. Gu T.H., Chen S.X., Zhu J.B., Song D.J., Guo J.Z., Hou H.M., Pharmacokinetics and Pharmacodynamics of diltiazem floating tablets. Acta Pharmacologica Sinica, 1992, 13: 527-531.

12. Nair M., Chien Y.M. Development of anticandidal delivery system: (II) Mucoadhesive devices for prolonged drug delivery in the oral cavity. Drug Development and Industrial Pharmacy, 1996, 22 (3), 243-253.

13. Swarbrick J., Boylan J.C., Encyclopedia of Pharmaceutical Technology, New York: Marcel Dekker Inc, 1994 (10), 142.

14. Chueh H.R., Zia H., Rhodes C.T., Optimization of sotalol and bioadhesive extended-release tablet formulations. Drug Development and Industrial Pharmacy, 1995, 21 (15), 1725-1747.

15. Altaf S.A., Yu K, Parasrampuria J, Friend D.R. Guar gum-based sustained release diltiazem, Pharmaceutical Research, 1998, 15(8), 1196-1201.

16. During T., Fassihi R., Guar based monolithic matrix system: Effect of ionizable and nonionizable substances and excipients on gel dynamics and release kinetics. Journal of Controlled Release, 2002, 80, 45-56.

17. Davis S.S. The design and evaluation of controlled-release systems for the gastrointestinal tract. In: Anderson J.M., Kim S.W., Advances in Drug Delivery Systems, Elsevier Science Publishers, New York, 1986, 27.

18. The United State Pharmacopoeia and the National formula, 26th ed., The United States pharmacopial convention. Inc, Washington, 2003.

19. Machida Y., Inoye K., Tokumura T., Iwata M., Nagai T., Preparation and evaluation of intra gastric buoyant preparations, Drug Design Delivery, 1989, 15, 155-161.

20. Menon A., Ritschel A., Sakr A., Development and evaluation of a monolithic floating dosage form for furosemide, Journal of Pharmaceutical Sciences, 1994, 83: 232-245.

21. Salsa T., Veiga G., Pina M.E., Oral controlled release dosage form. I. cellulose ether polymers in hydrophilic matrixes. Drug Development and Industrial Pharmacy, 1997, 23(9): 292-301.

22. Baumgartner S., Krist J., Vrecer F., Vodopivec P., Zorko B., Optimization of floating matrix tablets and evaluation of their gastric residence time. International Journal of pharmacy, 2000, 195, 125-135.

23. Shoufeng L., Senshang L., Bruce P., Daggy H., Mirchandani L., Yiew C., Effect of formulation variables on the floating properties of gastric floating drug delivery system. Drug Development and Industrial Pharmacy, 2002, 28(7): 783-793.

24. Praveen K., Roop K.K., Suraj P.A., Evaluation of guar gum in the preparation of sustained release matrix tablet. Drug Development and Industrial Pharmacy, 1998, 24 (11): 1095-1099.

25. Yu K., Altat S, Parasrampuria J., Friend D.R., Sustained release ketoprofen: formulation development. Proceed International Symposium Control Release Bioactive Materials, 1997: 16-17.

26. Bahalla H.L., Sanzgiri Y.D., An improved controlled release tablet of salbutamol sulphate. Indian Journal of Pharmaceutical Sciences, 1987, 49: 22-25.

27. Dortung B., Ozer L., Uyanik N., Development and in vitro evaluation of a buccoadhesive pindolol tablet formulation. Drug Development and Industrial Pharmacy, 1998, 24(3): 281-288.

28. Rajesh K., Suraj P., Alka A. Mucoadhesive buccal tablets of clotrimazole for oral candidiasis, Drug Development and Industrial Pharmacy, 1997, 23(8): 831-837.

29. Juarez H., Rico G., Villafuerte L., Influence of admixed carboxymethylcellulose on release of 4-aminopyridine from hydroxypropyl methylcellulose matrix tablets. International Journal of Pharmaceutics, 2001, 216 (1-2): 115-125.

30. Sinha V.R., Mittal B.R., Bhutani K.K., Kumria R., Colonic drug delivery of 5-flurouracil: an in vitro Evaluation. International Journal of Pharmaceutics, 2004, 269 (1): 101-108.

31. Saravanan M., Sri Nataraj K., Ganesh K.S., HPMC based cephalexin extended release tablets: influence of tablet formulation, hardness and storage on in vitro release kinetics. Chemical and Pharmaceutical Bulletin, 2003, 51 (8): 978-83.

33. Velasco M.V., Ford J.L., Rowe P., Rajabi-Siahboomi A.R., Influence of drug: HPMC ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. Journal of Controlled Release, 1999, 57: 75-85.