Available online on 15.10.2022 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Research Article

Development and Characterization of Floating Microspheres of Dexrabeprazole Sodium for the Treatment of Peptic Ulcer

Ragini Sahu, Sarang Jain

Rajiv Gandhi College of Pharmacy, Rajharsh Colony, Kolar Rd, Sankhedi, Bhopal, MP, 462042, India

Article Info:

Article History:

Received 03 August 2022
Reviewed 14 Sep 2022
Accepted 21 Sep 2022
Published 15 Oct 2022

Cite this article as:

Sahu R, Jain S, Development and Characterization of Floating Microspheres of Dexrabeprazole Sodium for the Treatment of Peptic Ulcer, Journal of Drug Delivery and Therapeutics. 2022; 12(5-S):20-26

DOI: http://dx.doi.org/10.22270/jddt.v12i5-s.5616

*Address for Correspondence:

Ms. Ragini Sahu, Asst. Professor, Rajiv Gandhi College of Pharmacy, Rajharsh Colony, Kolar Rd, Sankhedi, Bhopal, MP, 462042

Abstract

Dexrabeprazole sodium (DEX) is R (+)-isomer of rabeprazole. DEX has been used in the treatment of gastroesophageal reflux disease by suppressing gastric acid secretion. It acts as a proton pump inhibitor of the H+ /K+ ATPase enzyme. The purpose of this research was to prepare a floating drug delivery system of DEX. The floating microspheres can be prepared for the improvement of absorption and bioavailability of DEX by retaining the system in the stomach for prolonged period of time. Floating microspheres of DEX were prepared using different polymers like ethyl cellulose, hydroxy propyl methyl cellulose by solvent diffusion-evaporation method. The drug to polymer ratio used to prepare the different formulations was 1:7. The prepared floating microspheres were characterized for shape and surface morphology, size, percent drug loading, floating behavior, percentage yield and *in vitro* drug release. Formulation F1 showed good results with respect to the various evaluation parameters among various batches (F1-F8). The particle size increased with increase in polymer concentration. The drug entrapment efficiency was increased with increase in concentration of polymers. Buoyancy and the *in vitro* drug release decreased with respect to increase in concentration of polymers. *In-vitro* release and release kinetics data was subjected to different dissolution models. It was concluded that developed floating microspheres of DEX offers a suitable and practical approach for prolonged release of drug over an extended period of time and thus oral bioavailability, efficacy and patient compliance is improved.

Keywords: Dexrabeprazole sodium, Floating drug delivery system, Microspheres, Solvent diffusion-evaporation method

INTRODUCTION

Oral rout of administration is the most convenient and widely used method of drug administration and the development of stomach specific oral controlled-release drug delivery systems is a challenging job due to the variation of pH in different segments of the gastrointestinal tract, the fluctuation in gastric emptying time and the difficulty of localizing an oral delivery system in a selected region of the gastrointestinal tract. Rapid gastrointestinal transit can prevent the absorption of complete drug in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine[1,2]. To overcome the above discussed issues, many types of oral controlled drug delivery systems having prolonged gastric residence times have been reported such as: floating drug dosage systems (FDDS)[3-7], swelling or expanding system[8], mucoadhesive systems[9,10], modified-shape systems[11], high-density systems and other delayed gastric emptying devices[12]. FDDS have lower density than gastric fluids and thus remain buoyant in the stomach fluid without affecting the gastric emptying for a prolonged period of time. While the system is floating in the gastric fluid, the drug is released slowly from the system at a desired rate. Materials used for FDDS include carbon dioxide gas-forming agents (carbonate or bicarbonate compounds) [8, 13], highly swellable hydrocolloids and light mineral oils[14, 15]. Multiple unit systems and floating systems prepared by solvent evaporation methods have also been developed[12, 16-20]. However, it has been shown that products based on a multiple unit system comprising many small units have advantages over single -unit preparations such as matrix tablets[21]. The gastric emptying of multiple unit dosage forms occur gradually, in a more consistent manner, with less individual variation[2, 22]. Multiple unit dosage forms also have the potential to distribute widely over a large area in the stomach and small intestine, thus yielding a more predictable drug release by suppressing the effect of many variables in the gastrointestinal environment. As multiple unit dosage forms consist of many small units, less risk of dosage dumping is expected[23]. Chemically, Dexrabeprazole sodium is R (+)-isomer of rabeprazole (2-[[[4-(3-methoxypropoxy)- 3-methyl-2-pyridinyl]-methyl] sulfinyl] 1Hbenzimidazole). It is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the gastric H+ K+ ATPase enzyme system at the secretory surface of the gastric parietal cell[24, 25]. Floating microspheres are one of the multiparticulate delivery system and are prepared to obtain prolonged or controlled drug delivery to improve bioavailability and to target drug to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing site effects, decreasing dosing frequency and improving patient compliance[26].

MATERIAL AND METHODS

Material

Dexrabeprazole sodium was generously supplied as a gift samples by Bioplus Life Science, Bangalore. Ethyl Cellulose

and H.P.M.C. K4 were the gift samples obtained from Mapromax, Life sciences Pvt. Ltd., Dehradun (India). Dichloromethane, ethanol and isopropyl alcohol were purchased from E. Merck (India) Ltd., Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

Methods

Preformulation studies

Determination of λ_{max} of DEX

Accurately weighed 10 mg of drug was dissolved in 10 ml of Distilled water in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with Distilled water. Prepare suitable dilution to make it to a concentration range of 5-25µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+).

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical assortment were comparing with those of DEX pure drug. Samples was assorted comprehensively through 100mg potassium bromide IR powder as well as compacted under vacuum at a pressure of concerning 12 psi for 3 minutes. The ensuing disc was mounted in an appropriate holder in Brukers Alpha IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preparation of floating microsphere of DEX

Floating microsphere containing DEX was prepared using emulsion solvent diffusion technique. The drug to polymer ratio used to prepare the different formulations was 1:7. The polymer content was a mixture of ethyl cellulose and hydroxypropylmethylcellulose (HPMC) as shown in table 1. The drug polymer mixture is dissolved in a mixture of ethanol (8 ml) and dichloromethane (8 ml) was dropped in to 0.75% polyvinyl alcohol solution (200 ml). The solution was stirred with a propeller-type agitator at 40°C temperatures for 1 hour at 300 rpm. The formed floating microspheres were passed through sieve no.12 and washed with water and dried at room temperature in a desiccator[27].

Table 1 Formulations of the floating microspheres of DEX

Sr. No	Formulation Code	DEX (gm)	EC (gm)	HPMC (gm)
1	F_1	0.1	0.8	0.1
2	F_2	0.1	0.7	0.2
3	F_3	0.1	0.6	0.3
4	F_4	0.1	0.5	0.4
5	F_5	0.1	0.4	0.5
6	F_6	0.1	0.3	0.6
7	F_7	0.1	0.2	0.7
8	F_8	0.1	0.1	0.8

Evaluation of microspheres

Particle size determination

The particle size of formulation was determined by optical microscopy using a calibrated ocular micrometer.

Floating behavior of floating microsphere

100 mg of the floating microsphere were placed in 0.1 N HCI. The mixture was stirred with paddle at 100 rpm. The layer of buoyant microspheres was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microspheres were dried in a desiccator over night. The percentage of microspheres was calculated by the following equation:

% floating microsphere = Weight of floating microsphere/ Initial weight of floating microsphere x 100

Drug entrapment

The various formulations of the floating microspheres were subjected for drug content. 50 mg of floating microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. The absorbance was measured at 260.0 nm against blank. The percentage drug entrapment was calculated as follows.

% Drug entrapment =Calculated drug concentration/ Theoretical drug concentration x 100

Percentage yield

The prepared microspheres with a size range of 609-874 µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

Shape and surface morphology

In order to examine the surface morphology, the formulations were viewed under scanning electron microscopy. The samples for SEM were prepared by lightly sprinkling the floating microspheres powder on a double adhesive tape, which stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300Å using a sputter water. The samples were then randomly scanned for studying surface morphology but show the images of coating to prove internal surface[28].

In-vitro release studies

The drug release rate from floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples were treated with methyl orange and analyzed spectrophotometrically at 260 nm to determine the concentration of drug present in the dissolution medium. Percentage cumulative drug release was calculated[29].

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation

(Plotted as Log cumulative percentage of drug released vs Log time).

To study the release kinetics of Famotidinefrom the Floating microspheres the release data was fitted to these three equations

Zero order equation: When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

$Q_t = k_0.t$ ..... (1)

Where Q_t is the percentage of drug released at time t and k_0 is the release rate constant;

First order equation:-

In $(100-Q_t) = In\ 100- k_I.t$ ..... (2)

Where k_I is the release rate constant;

Higuchi's equation (Wagner, 1969):-

$Q_t = k_H.t^{1/2}$ ..... (3)

Where K_H is the Higuchi release rate constant

Korsemeyer-Peppas:-

The curves plotted may have different slopes, and hence it becomes difficult to exactly pin-point which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, data were also analyzed using Korsemeyer's equation.

$Q_t/Q_\infty = k_{KP}.t^n$

Where Q_t/ Q_∞ is the fraction of drug released at time t, k_{KP}a constant compromising the structural and geometric characteristics of the device and n is the release exponent.

The slope of the linear curve gives the 'n' value. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of 'n' gives an indication of the release mechanism. When n = 1, the release rate is independent of time (typical zero order release / case II transport); n = 0.5 for Fickian release (diffusion/ case I transport); and when 0.5 < n < 1, anomalous (non-Fickian or coupled diffusion/ relaxation) are implicated. Lastly, when n > 1.0 super case II transport is apparent. 'n' is the slope value of log M_t/M_∞ versus log time curve[30-32].

RESULTS AND DISCUSSION

Solubility of DEX was freely soluble in ethyl acetate, chloroform and ethanol, insoluble in n- hexane and ether, soluble in water and methanol. The melting point and partition coefficient of DEX was found to be 220-223°C and 1.17 respectively. λ_{max} of DEX was found to be 260.0 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25µg/ml Fig.1. Identification of DEX was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification Fig. 2. The floating microspheres of DEX were prepared by solvent diffusion-evaporation method. Percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of different formulation was in range of 56.84 - 82.87% Table 2. The drug entrapment efficacies of different formulations were in range of 48.47-76.19 % w/w as shown in Table 2. Drug entrapment efficacy slightly decrease with increase HPMC content and decreased EC ratio in Microspheres. This is due to the permeation characteristics of HPMC that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of DEX microspheres. F1 microspheres entrapped maximum amount of the drug. Particle size was determined by optical microscopy method. It plays important role in floating ability and release of drug from microsphere. If size of microspheres is less than 500 µm release rate of drug will be high and floating ability will reduce, white microspheres ranging between 200µm- 500µm, the floating ability will be more and release rate will be in sustained manner. The mean particle size of DEX microsphere was in range 210-264 µm as shown in Table 3. DEX microsphere was dispersed in 0.1 HCl as simulate gastric fluid. Floating ability of different formulation was found to be differed according to EC and HPMC ratio. F_1-F_4 formulations showed best floating ability (91.47-72.97%) in 6 hours. F_5-F_7 formulation showed less floating ability (66.12-45.09%) as showed in Table 4. The floating ability of microsphere is decreased by increasing the HPMC ratio. Shape and surface characteristic of Dexrabeprazole sodium microspheres examine by Scanning Electronic Microscopy analysis (Fig. 3). Surface morphology of formulation examines at different magnification, which illustrate the smooth surface of floating microspheres. The drug release from floating microspheres was found to be 82.857% at the end of 8 h for F1 Table 5 & Fig. 4. The *In-vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Korsmeyer's was maximum i.e 0.928 hence indicating drug release from formulations was found to follow Korsmeyer's models kinetics Table 6, 7 & Fig. 5-8.

Table 2 Percentage yield and % drug entrapment for different formulation

Formulation	Percent Yield (%)	Drug entrapment (% w/w)
F_1	82.87	76.19
F_2	78.53	70.59
F_3	76.47	66.23
F_4	71.56	64.76
F_5	69.31	61.01
F_6	66.03	57.38
F_7	56.84	48.47

Table 3 Mean particle size of different formulations

Formulation code	Mean particle size (µm)
F_1	212±12
F_2	225±21
F_3	264±23
F_4	236±25
F_5	242± 24
F_6	244±40
F_7	210±23

Table 4 Percentage buoyancy for different formulation

Formulation	1 hour	2 hours	4 hours	6 hours
F_1	98.41	97.08	93.23	91.47
F_2	98.11	95.58	92.17	87.34
F_3	98.54	95.64	85.34	78.45
F_4	99.54	92.49	80.57	72.97
F_5	98.72	91.95	73.49	66.12
F_6	98.45	86.62	65.14	57.76
F_7	88.34	75.41	56.04	45.09

Table 5 Release study data of formulation F1-F7

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7
0.5	16.429	15.000	13.571	14.286	17.857	16.429	14.286
1	25.714	17.857	17.143	17.857	27.143	25.000	22.143
1.5	28.571	25.714	22.857	25.714	32.143	29.286	32.143
2	53.571	30.000	28.571	30.000	40.000	40.000	35.714
3	65.000	55.714	41.429	36.429	55.714	49.286	53.571
4	72.143	70.000	46.429	46.429	62.857	70.000	48.571
6	82.143	75.000	70.000	63.571	66.429	82.143	55.714
8	82.857	75.714	74.286	75.000	80.000	84.286	80.143

Table 6 Release kinetics of optimized formulation F-1

Time (Hrs.)	% CDR	Log T	Root T	Log % cum. drug remain to be release	Log cum. % drug release	cum. % drug remain to be released
0.5	16.429	-0.30103	0.70710678	1.9220556	1.2156111	83.571
1	25.714	0	1	1.87090697	1.4101696	74.286
1.5	28.571	0.176091259	1.22474487	1.85387457	1.4559254	71.429
2	53.571	0.301029996	1.41421356	1.66678933	1.7289298	46.429
3	65	0.477121255	1.73205081	1.54406804	1.8129134	35
4	72.143	0.602059991	2	1.44493434	1.8581942	27.857
6	82.143	0.77815125	2.44948974	1.2518085	1.9145706	17.857
8	82.857	0.903089987	2.82842712	1.23408683	1.9183292	17.143

Table 7 Comparative study of regression coefficient for selection of optimize formulation F-1

Zero order		First order	Higuchi	Korsmeyer
r^2	0.808	0.916	0.906	0.928

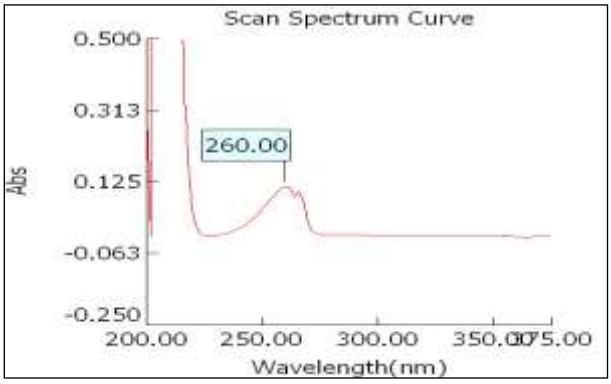

Figure 1 λmax of dexrabeprazole sodium

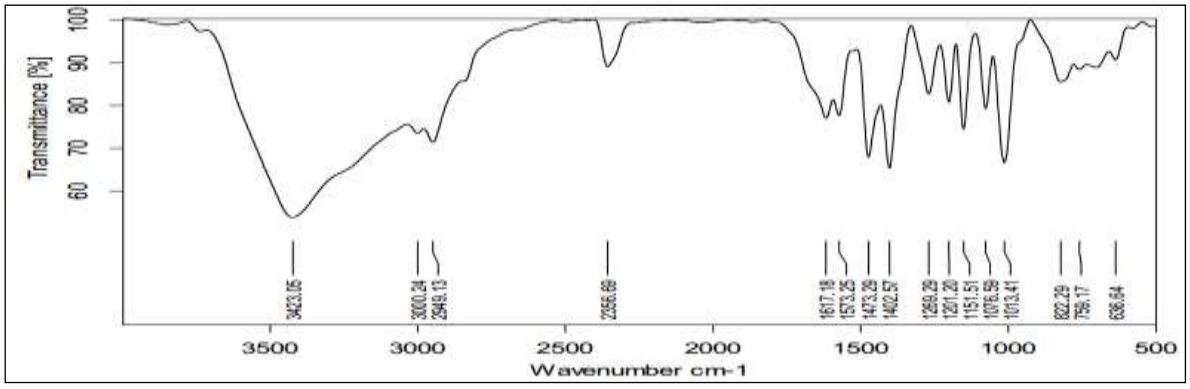

Figure 2 FT-IR Spectrum of pure drug DEX

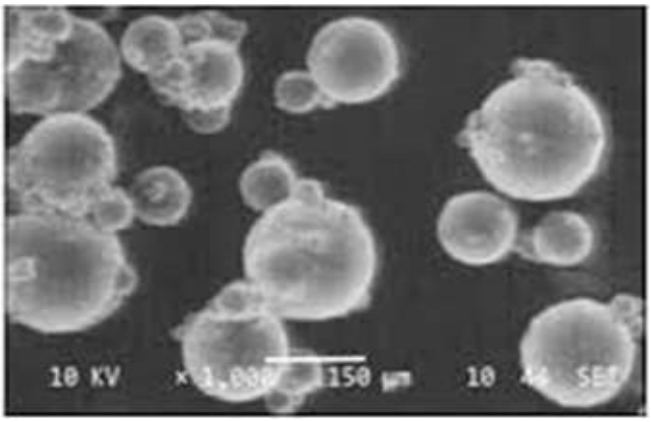

Figure 3 Scanning electronic microscopy image of optimized formulation F-1

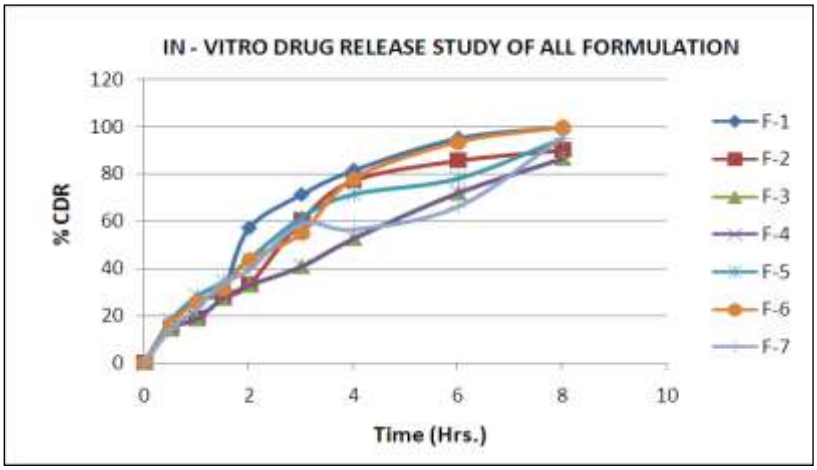

Figure 4 Graph of release study of formulation F1-F7

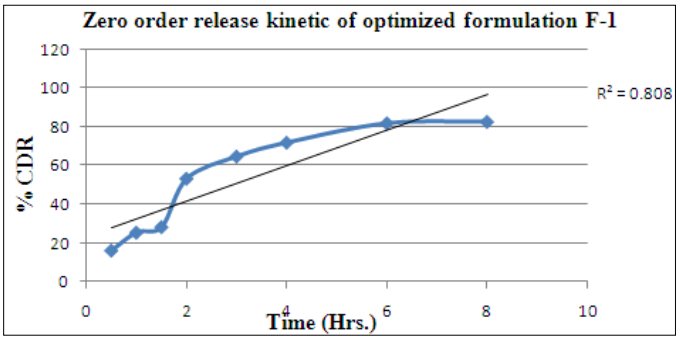

Figure 5 Graph of Zero order release kinetics of F-1

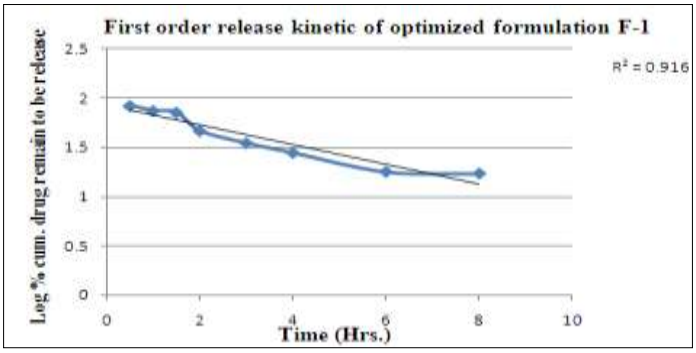

Figure 6 Graph of First order release kinetics of F-1

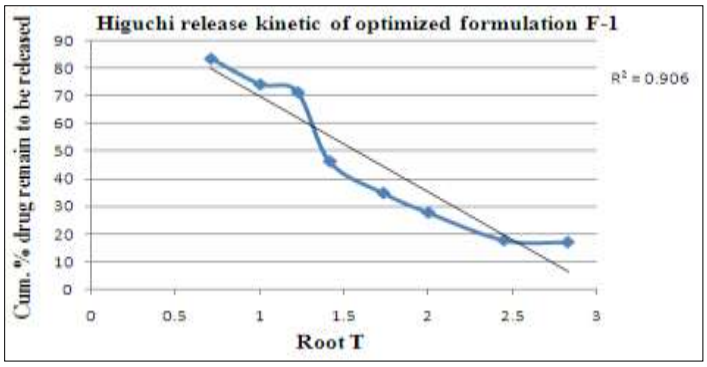

Figure 7 Graph of Higuchi order release kinetics of F-1

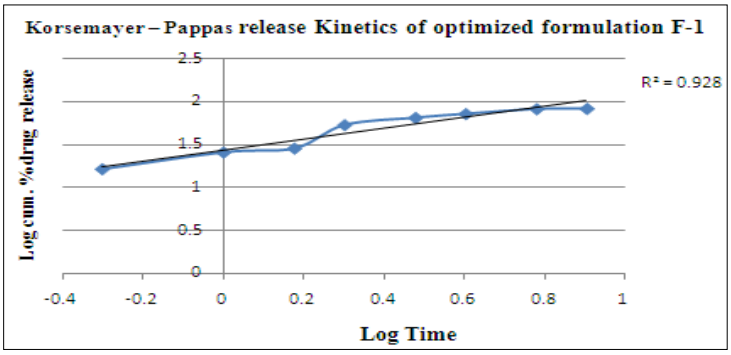

Figure 8 Graph of Korsmeyer- pappas release kinetics of F-1

CONCLUSION

Floating microspheres of DEX as a gastro retentive drug delivery system specifically control the release rate of drugs to a particular site and facilitate an enormous effect on health care. Microspheres of different size and drug content could be obtained by varying the formulation variables. On the basis of drug release, percentage yield, drug entrapment, percentage buoyancy and floating lag time F1 could be considered as promising formulations. Thus, the prepared floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

REFERENCES

1. Kaushik K, Chaurasia D, Chaurasia H, Mishra SK, Bhardwaj P. Development and characterization of floating alginate beads for gastroretentive drug delivery system. Acta Pharma Sci. 2011; 53(4): 551-562.

2. Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and in vitro-in vivo evaluation in healthy human volunteers. Eur J Pharm Biopharm. 2010; 74(2):332-339. https://doi.org/10.1016/j.ejpb.2009.11.010

3. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm. 2000; 195(1-2):125-135. https://doi.org/10.1016/S0378-5173(99)00378-6

4. Bulgarelli E, Forni F, Bernabei MT. Effect of matrix composition and process conditions on casein-gelatin beads floating properties. Int J Pharm. 2000; 198(2):157-165. https://doi.org/10.1016/S0378-5173(00)00327-6

5. Davoudi ET, Noordin MI, Kadivar A, Kamalidehghan B, Farjam AS, Javar HA. Preparation and characterization of a gastric floating dosage form of capecitabine. Biomed Res Int. 2013. https://doi.org/10.1155/2013/495319

6. Asati S, Jain S, Choubey A, Bioadhesive or mucoadhesive drug delivery system: a potential alternative to conventional therapy, Journal of Drug Delivery and Therapeutics, 2019; 9(4-A):858-867

7. Garg R, Gupta G. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res. 2008; 7(3):1055-1066. https://doi.org/10.4314/tjpr.v7i3.14691

8. Chen J, Park K. Synthesis of fast-swelling, superporous sucrose hydrogels. Carbohyd Polym. 2000; 41(3):259-268. https://doi.org/10.1016/S0144-8617(99)00144-7

9. Shaikh R, Singh TRR, Garland MJ, W oolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 2011; 3(1):89-100. https://doi.org/10.4103/0975-7406.76478

10. Boddupalli BM, Mohammed ZNK, Nath RA, Banji D. Mucoadhesive drug delivery system: an overview. J Adv Pharm Technol Res. 2010; 1(4):381-387. https://doi.org/10.4103/0110-5558.76436

11. Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, H offman M, Maincent P. Evaluation of peroral silicone dosage forms in hymans by gamma-scintigraphy. J Control Release. 1999; 58(2):195-205. https://doi.org/10.1016/S0168-3659(98)00154-0

12. Rouge N, Allémann E, Gex-Fabry M, Balant L, Cole ET, Buri P, et al. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multiple-unit capsule and an immediate-release tablet containing 25 mg atenolol. Pharm Acta Helv. 1998; 73(2):81-87. https://doi.org/10.1016/S0031-6865(97)00050-2

13. Prajapati PH, Nakum VV, Patel CN. Formulation and evaluation of floating matrix tablet of stavudine. Int J Pharm Investig. 2012; 2(2):83-89. https://doi.org/10.4103/2230-973X.100047

14. Chaturvedi K, Umadevi S, Vaghani S. Floating matrix dosage form for propranolol hydrochloride based on gas formation technique: development and in vitro evaluation. Sci Pharm. 2010; 78(4):927-939. https://doi.org/10.3797/scipharm.0909-02

15. Murata Y, Sasaki N, Miyamoto E, Kawashima S. U se of floating alginate gel beads for stomach-specific drug delivery. Eur J Pharm Biopharm. 2000; 50(2):221-226. https://doi.org/10.1016/S0939-6411(00)00110-7

16. Jagtap YM, Bhujbal RK, Ranade AN, Ranpise NS. Effect of various polymers concentrations on physicochemical properties of floating microspheres. Indian J Pharm Sci. 2012; 74(6):512-520. https://doi.org/10.4103/0250-474X.110578

17. Jain AK, Jain CP, Tanwar YS, Naruka PS. Formulation, characterization and in vitro evaluation of floating microspheres of famotidine as a gastro retentive dosage form. Asian J Pharm. 2009; 3(3):222-226. https://doi.org/10.4103/0973-8398.56302

18. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm. 2001; 220(1-2):13-21. https://doi.org/10.1016/S0378-5173(01)00574-9

19. Dhakar RC, Maurya SD, Sagar BPS, Bhagat S, Prajapati SK, Jain CP, Variables influencing the drug entrapment efficiency of microspheres: A pharmaceutical review, Der Pharmacia Lettre, 2010; 2(5):102-116

20. Singh A, Patel VJ, Jain DK, Sharma PC, Gupta AK, Sharma AK, Rajak H. Histone deacetylase inhibitors: current status in treatment of leukemia. Curr Res Pharm Sci.2013; 03 (04):102-107.

21. Pandya N, P andya M, Bhaskar VH. Preparation and in vitro characterization of porous carrier-based glipizide floating microspheres for gastric delivery. J Young Pharm. 2011; 3(2):97-104. https://doi.org/10.4103/0975-1483.80292

22. Jagdale SC, Agavekar AJ, Pandya SV, Kuchekar BS, Chabukswar AR. Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. AAPS PharmSciTech. 2009; 10(3):1071-1079. https://doi.org/10.1208/s12249-009-9300-8

23. Hussain MN, M asum MAA, Akhter S, Sharmin F, Reza MS. Formulation and evaluation of gastro retentive floating tablets of simvastatin using hydrophilic rate retardant. Bangladesh Pharm J. 2012; 15(2):119-126. https://doi.org/10.3329/bpj.v15i2.12575

24. Jain N, Jain R, Jain DK, Patel VK, Jain SK. Development and validation of a green bioanalytical method for the determination of sparfloxacin in pharmaceutical dosage form and human plasma by RP-HPLC. Int Res J Pharm. 2016; 7(6):91-95. https://doi.org/10.7897/2230-8407.07671

25. Chitlange SS, Mulla AI, Pawbake GR, Wankhede SB. Simultaneous spectrophotometric estimation of dexrabeprazole and domperidone in capsule dosage form. Int J Pharm Qual Assur. 2010; 2(2):31-34.

26. Haznedar S, Dortunc B. Preparation and in vitro evaluation of eudragit microspheres containing acetazolamide. Int J Pharm. 2004; 269(1):131-140. https://doi.org/10.1016/j.ijpharm.2003.09.015

27. Kawashima Y, Niwa T, Takechi H, Hino T, Itoh Y. Hollow microspheres for use as floating controlled drug delivery systems in the stomach. J Pharml Sci. 1992; 81:135-40. https://doi.org/10.1002/jps.2600810207

28. Jagdale S, Agavekar A, Pandya S, Kuchekar B, Chabukswar A. formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. AAPS Pharm Sci Tech. 2009; 10:3. https://doi.org/10.1208/s12249-009-9300-8

29. Kim BK, Hwang SJ, Park JB. Preparation and characterization of drug loaded polymethacrylate microspheres by an emulsion solvent evaporation method. J Microencap. 2002; 19:811-822. https://doi.org/10.1080/0265204021000022770

30. Brahamankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics e a treatise, pharmacokinetics: basic consideration. 2nd ed. Vallabh Prakashan; 2009. pp. 240e3.

31. Higuchi T. Mechanism of sustained action medication, theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963; 52:1145-9. https://doi.org/10.1002/jps.2600521210

32. Korsmeyer RW, Gumy R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymer. Int J Pharm. 1983; 15:25-35. https://doi.org/10.1016/0378-5173(83)90064-9