Past Decade Attempts on Gastro Retentive Microspheres Using Factorial Design: A Comprehensive Literature

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ABSTRACT

The main intention of floating microspheres is to elevate gastro-retentive time, there by drug release and bioavailability. Floating drug delivery systems glide on gastric fluid for an extended time without leaving the stomach and give good accessibility of the drug systemically and good duration of action for the prolonged period of time. Gastro-retentive microspheres are preferred for local action, local absorption, and preventing drug deterioration at the stomach. This article was made by pearly referring to published research papers of both online and offline journals on gastro retentive microspheres made by factorial design. The authors succeeded in collecting the information about the past decade of work done on gastro retentive drug delivery systems using factorial design. The authors from this study conclude that factorial design is an appreciable technique in the optimization of the gastro retentive dosage form in the form off microspheres for the drug delivery for the extended period of time.

Key Words: *Stomach, Target, Dosage form, Drug release*

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INTRODUCTION

The oral route is harmless and real for decades for drug delivery [1, 2]. The drug liberates by this traditional oral route has fluctuation in the sum of medication reaching the blood with time as it has to pass different pH zones of the gut [3]. Novel approaches were made to solve this issue, among them gastro retentive systems gaining importance from researchers and formulation development scientists [4, 5]. Among the gastro, retentive systems microspheres are preferred for their ease in the making, flow properties (easy to fill in hard gelatin capsules). Floating drug delivery is intended to hold the drug in the stomach. Drugs with shorter half-lives that are readily absorbed in GIT are highly detached from the circulation of the serum [6, 7]. To resolve these difficulties, the oral managed drug delivery mechanism has risen as they liberate the drug into the GIT for longer periods and retain a steady concentration of medication in the serum. In the gastric area, the gastroprotective dosage type may last for few hours and thus significantly increase the drug GRT to improve bioavailability, minimize drug waste and improve the solubility of drugs with low solubility. Floating microspheres are empty spherical particles deprived of a centre, in a stringent sense with free-flowing particles [8] oscillating in size from 1 to 1000μm.

Types of gastro retentive dosage forms

Floating tablets

These are low-density tablets which buoyant at the upper part of the stomach owing to their low density. These may be Effervescent floating tablets were made with swellable polymers and diverse effervescent compounds (combination of citric acid/tartaric acid with Sodium

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bicarbonate). When these tablets contact with the gastric fluid liberates CO_2 that is captured in a swollen polymer that buoyant in gastric fluid. On the otherhand, the Non-effervescent systems, which contain swellable polymers, on swelling their density attains <1, which makes the tablets buoyant [9, 10] on the stomach.

Floating microspheres

The microspheres buoyant on gastric fluid and retain in the stomach for sufficient time and have site-specific delivery [11, 12].

Mucoadhesive microspheres

The microspheres remain in the stomach and liberate the drug by binding with gastric mucosa [13, 14].

Mucoadhesive tablets

These are conventionally compressed tablets with mucoadhesive polymers that retain in the stomach and liberates the drug by binding with gastric mucosa [15, 16].

High-density microspheres

The microspheres remain in the stomach and liberate the drug by sinking at the bottom of the stomach as it contains materials whose density is more than gastric fluid. These systems also have site-specific drug delivery at the stomach [17].

Expanding systems

These systems when ingested swells and reach to bigger size which is larger that cannot be transferred across the pyloric sphincter of the stomach, they retain in the stomach and have drug delivery at the stomach. **Figure 1** indicates the various locations for gastro-specific dosage forms [18].

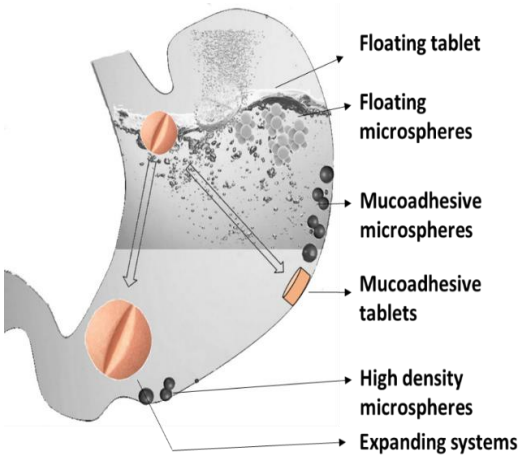

Figure 1. An exemplified way of gastro retentive dosage forms

Gastro-retentive microspheres

These delivery systems were retained in the stomach by the mechanism of low density/high density/gas generating/mucoadhesive methods [19]. The merits and pitfalls of these systems [20-22] were elucidated here.

Advantages

- Avail local therapy in the stomach
- Avoids the liberation of the drugs into the small intestine where they may get deteriorated/destroyed
- A factorial design is necessary when relations may be existing to dodge ambiguous assumptions.
- Factorial designs let the things of a factor be projected at numerous levels of the diverse factors.
- Optimized discharge of short t½ drugs, with reduced frequency and patient compliance.
- They are more competent than one-factor-at-a-time or trial and error try-outs.
- Stabilized beneficial effects of drugs that are used for chronic ailments
- Upsurge in bioavailability and restorative capability of drugs and slashed dosage cost.

Pitfalls

- Changeable gastro adhesiveness due to regular renewal of gastric mucus wall
- Gastro retentive hydrogel systems may take more spells to swell.
- Meal's intake may meddle with gastro retention.
- Need regular intake of fluid for making the dosage form to retain in the stomach.
- Not fit for drugs with solubility issue at stomach pH, gastric irritation, degradation at the stomach, colon-specific drug delivery.

Factorial design used in optimizing gastroprotective microspheres

Numerous tests include the investigation of the impacts of at least two components. Factorial plans are generally productive for this sort of examination. In a factorial plan, all potential mixes of the levels [23] of the components are examined in every replication. On the off chance that there are degrees of factor A, and b levels of factor B, at that point each imitates contains all stomach muscle treatment blends. The principle impact of a factor is characterized [24] to be the adjustment accordingly created by an adjustment in the level of a factor. The fundamental impact of A_n is the distinction between the normal reaction at A_1 and A_2.

The factorial plan, just as working on the cycle and making research less expensive, permits many degrees of investigation. Just as featuring the associates among the

factors, it likewise permits the effects of controlling a solitary variable to be detached and dissected separately [25]. Independent and dependant variables adopted in recent years as explained in **Table 1**.

Table 1. Drug and polymers used in making gastro retentive microspheres by factorial design

Drug	Polymer/ main excipient	Design	Independent Variable	Dependant Variable	Reference
Repaglinide	Hydroxypropyl methylcellulose (HPMC), Polyethylene glycol 400, and Ethyl Cellulose (EC)	3^2 FFD	Stirring speed (X_1), The concentration of Polymer Ratio (X_2)	%yield (Y_1), Entrapment efficiency (EE) (Y_2), In-vitro Buoyancy (Y_3), and %Drug release (DR) (Y_4)	Patel *et al.*, 2020 [26]
Olanzepine	Carbopol 974P, Sodium Alginate and Calcium chloride (Ca Cl_2)	3^2 FFD	Stirring speed (X_1) and Concentration of Polymer (X_2)	Drug content (Y_1), EE (Y_2), % mucoadhesion (MA) (Y_3) and *in vitro* DR (Y_4)	Deshmukh *et al.*, 2020 [27]
Metronidazole	Sodium alginate, carbopol 934P, and Ca Cl_2	3^2 FFD	The concentration of Sodium alginate (X_1) and the Concentration of Polymer Carbopol 934P (X_2)	%yield (Y_1), EE (Y_2), Particle size (PS) (Y_3), Swelling index (SI) (Y_4), %MA (Y_5), and DR (Y_6)	Paul *et al.*, 2019 [28]
Valsartan	Carbopol 934P and EC	Box Behnken Design (BBD)	Amount of EC (X_1), Amount of carbopol 934P (X_2), and Stirring speed (X_3)	EE (Y_1), DR at 1h (Q_1h) (Y_2), t90% (Y_3), and %MA (Y_4)	Lal *et al.*, 2019 [29]
Metoprolol tartrate	EC	2^3 FFD	EC concentration (X_1) and Stirring speed (X_2)	EE (Y_1) and PS (Y_2)	Bhavani *et al.*, 2019 [30]
Cinnarizine	Eudragit RS, Eudragit RL and Iron oxide	3^2 FFD	Eudragit RS or RL (X_1) and Iron oxide (X_2) Concentrations	PS (Y_1), EE (Y_2), MA (Y_3), zeta potential (Y_4), and $t_{90\%}$ (Y_5)	Singh *et al.*, 2017 [31]
Fluoxetine HCl	Chitosan	3^2 FFD	Amount of Polymer (X_1) and Speed (X_2)	EE (Y_1), % MA (Y_2), and % DR (Y_3)	Deshmukh *et al.*, 2017 [32]
Cefditoren pivoxel	HPMC K4M and EC	3^2 FFD	The total amount of polymer (X_1) and Concentration of EC (X_2)	% yield (Y_1), PS (Y_2), EE (Y_3) and Dissolution efficiency (Y_4)	Chilukala *et al.*, 2016 [33]
Amoxicillin	Carbopol 934 and EC	3^3 FFD	Polymer Concentration (X_1), Emulsifying agent concentration (X_2), and the stirring speed (X_3)	EE (Y_1) and PS (Y_2)	Hardenia *et al.*, 2016 [34]
Clotrimazole	Eudragit S100 and Sodium carboxymethyl cellulose (Na CMC)	BBD	Polymer amount (X_1), Surfactant concentration (X_2) and Stirring speed (X_3)	PS (Y_1) and EE (Y_2)	Rai *et al.*, 2016 [35]
Cimetidine	Sodium alginate, Na CMC, Xanthan gum, and Gum Kondagogu	3^2 FFD	Polymer concentration (X_1) and Sodium alginate concentration (X_2)	EE (Y_1), % MA (Y_2), and *in vitro* DR (Y_3)	Thulluru *et al.*, 2016 [36]
Sigagliptin	HPMC and PVP K30	3^2 FFD	Amount of Psyllium husk(X_1) and Amount of HPMC K4M(X_2)	*In vitro* DR (Y_1) and SI (Y_2)	Tandel *et al.*, 2016 [37]
Furosemide	Sodium alginate, Chitosan and Ca Cl_2	2^2FFD	Polymer concentration (X_1) and Sodium alginate concentration (X_2)	EE (Y_1), %MA (Y_2), DR (Y_3) and SI (Y_4)	Kumar *et al.*, 2016 [38]
Prochlorperazine	Chitosan and Glutaraldehyde	2^3 FFD	Amount of polymer (X_1), Feed flow rate (X_2), and Volume of Glutaraldehyde (X_3)	PS (Y_1) and EE (Y_2)	Shah 2015 [39]

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Praziquantel	Sodium alginate and Ca Cl_2	2^3 FFD	The amount of Drug: Polymer ratio (X_1) and the amount of Ca Cl_2 (X_2) and dropping height (X_3)	EE (Y_1), drug loading (Y_2), and PS (Y_3)	Anand *et al.*, 2014 [40]
Cefdinir	Sodium Tripoly Phosphate and Gum Karaya, Acetic acid	2^3 FFD	Gum Karaya in % (X_1), Sodium Tripoly Acetic Acid Phosphate in % (X_2) The acetic acid in % (X_3)	SI (Y_1), %yield (Y_2), Drug content (Y_3), EE (Y_4) and *n-Vitro* DR (Y_5)	Chandiran *et al.*, 2014 [41]
Ranitidine HCl	Chitosan	3^2 FFD	Stirring speed (X_1) and Polymer-to-Drug ratio (X_2)	PS (Y_1), SI (Y_2), EE (Y_3), %MA (Y_4) and *in Vitro* DR (Y_5)	Awasthi *et al.*, 2014 [42]
Acetazolamide	Eudragit RS100	BBD	Drug: polymer ratio (X_1), Surfactant concentration % (X_2), and Stirring rate (rpm) (X_3)	EE (Y_1), %DR after 6 h (Y_2) and PS (Y_3)	Abdallah *et al.*, 2014 [43]
Duloxetine HCl	Chitosan and Eudragit L-100	3^2 FFD	Polymer-to-drug ratio (X_1) and Stirring speed (X_2)	PS (Y_1), EE (Y_2), SI, %MA and DR up to 24 h (t_{24}) (Y_3)	Setia *et al.*, 2013 [44]
Carvedilol	EC and HPMC	3^2 FFD	The concentration of EC (X_1) and Stirring speed (X_2)	EE (Y_1), %DR at 10^{th} h (Y_2) and PS (Y_3)	Nila *et al.*, 2013 [45]
Cefpodoxime proxetil	Dioctyl sodium sulphosuccinate and Chitosan	3^2 FFD	Drug polymer ratio (X_1) and Glutaraldehyde (X_2)	EE (Y_1), SI (Y_2), % MA (Y_3) and Time for 50% drug dissolution (t50) (Y_4)	Nappinai *et al.*, 2013 [46]
Captopril	EC and Eudragit RL 100	3^2 FFD	The total amount of polymer (X_1) and % of EC (X_2)	$T_{50\%}$ (Y_1), $T_{80\%}$ (Y_2), release at 12 h (Y_2), release at 18 h (Y_3), and K of 1^{st} order (Y_4)	Gandhi *et al.*, 2012 [47]
Venlaflaxine HCl	EC, HPMC K4M and Eudragit RS100	2^3 FFD	Polymer-to-drug ratio (X_1) and Stirring speed (X_2)	%yield (Y_1), PS (Y_2), and EE (Y_3)	Senthil *et al.*, 2011 [48]
Atenolol	Carbopol 934P, Eudragit RL100, Span 80, Ethanol, and Petroleum ether	3^2 FFD	Drug to polymer ratio (Y_1) and drug to Polymer ratio (Y_2)	%MA (Y_1), EE (Y_2), and *In-vitro* DR (Y_3)	Natarajan *et al.*, 2011 [49]
Famotidine	HPMC K4M and Gelucire 43/01	3^2 FFD	The ratio of Gelucire 43/01 to HPMC K4M (X_1) and the type of filler (X_2)	Buoyancy lag time (Y_1), DR at 1h (Q_1) (Y_2), 6h (Q_6) (Y_3), and the 12h (Q_{12}) (Y_4)	Patel *et al.*, 2011 [50]
Nifedipine	Eudragit RL100 and Polyvinyl alcohol (PVA)	2^3 FFD	Eudragit concentration (X_1), PVA concentration (X_2), and drug/polymer ratio (X_3)	EE (Y_1) and *in-vitro* DR (Y_2)	Dehghan *et al.*, 2010 [51]
Propranolol HCl	Carbopol-934P and EC	3^2 FFD	Drug-to-polymer-to-polymer (X_1) and the Stirring speed (X_2)	%MA (Y_1), EE (Y_2), PS (Y_3), and the time required for 80 % DR (Y_4)	Patel *et al.*, 2010 [52]
Acyclovir	HPMC K4M and Psyllium husk	3^2FFD	Amount of Psyllium husk(X_1) and Amount of HPMC K4M(X_2)	DR 50% ($t_{50\%}$) (Y_1) and DR 70% ($t_{70\%}$) (Y_2)	Kharia *et al.*, 2010 [53]
Rosiglitazone maleate	EC and HPMC K100M	3^2 FFD	The concentration of EC (X_1) and Stirring speed (X_2)	EE (Y_1), %DR after 8 h (Y_2) and PS (Y_3)	Rao *et al.*, 2009 [54]

CONCLUSION

The factorial plan is more creative than the 1-factor A factorial plan is essential, when connections are available, to evade a deceptive end. Assessment of one factor at diverse levels of the other factor could yield determinations over a scope of conditions for the trial.

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REFERENCES

[1] Ashjaran A, Sheybani S. Drug Release of Bacterial Cellulose as Antibacterial Nano Wound Dressing. Int J Pharm Res Allied Sci. 2019;8(3):137-43.
[2] Al Zahrani S, Eid Alosaimi M, Alamrim AA, Alotaibi M, Almatar EA, Almanea BA. Association between knowledge and drug adherence in patients with hypertension in Saudi Arabia. Arch Pharm Pract. 2019;10(3):71-6.
[3] De Souza MP, Sábio RM, de Cassia Ribeiro T, Dos Santos AM, Meneguin AB, Chorilli M. Highlighting the impact of chitosan on the development of gastroretentive drug delivery systems. Int J Biol Macromol. 2020;159:804-22.
[4] Li Z, Zeng R, Yang L, Ren X, Maffucci KG, Qu Y. Development and Characterization of PCL Electrospun Membrane-Coated Bletilla striata Polysaccharide-Based Gastroretentive Drug Delivery System. AAPS Pharm Sci Tech. 2020;21(2):1-4.
[5] Lopes CM, Bettencourt C, Rossi A, Buttini F, Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. Int J Pharm. 2016;510(1):144-58.
[6] Ahad HA, Haranath C, Rahul Raghav D, Gowthami M, Naga Jyothi V, Sravanthi P. Overview on Recent Optimization Techniques in Gastro Retentive Microcapsules by Factorial Design. Int J Pharm Sci Res. 2019;10(9):247-54.
[7] Harsha SS, Ahad HA, Haranath C, Dasari RR, Gowthami M, Varam NJ, et al. Exfoliation Technique of Composing and Depictions of Clopidogrel Bisulphate Afloat Microspheres. J Evol of Med Dent Sci. 2020;9(14):1156-61.
[8] Chinthaginjala H, Gandla CB, Challa MR, Pradeepkumar B, Ahad HA. Formulation and in vitro Evaluation of Floating Tablets of Dicloxacillin Sodium Using Different Polymers. J Young Pharm. 2019;11(3):247.
[9] Li Q, Guan X, Cui M, Zhu Z, Chen K, Wen H, et al. Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing. Int J Pharm. 2018;535(1-2):325-32.
[10] Rawat S, Sangali S, Gupta A. Formulation and Evaluation of Floating Matrix Tablets of Acyclovir using 3 2 Factorial Design. Res J Pharm Dosage Forms Technol. 2018;10(1):1-9.
[11] Faizi SM, Rathi PN, Tajane SV, Burghate RM, Wasankar SR. Drug delivery to absorption window through floating microspheres: A Review. Res J Pharm Dosage Forms Technol. 2012;4(3):II.
[12] Deepa M, Karthikeyan M. Cefpodoxime proxetil floating microspheres: formulation and in vitro evaluation. Iran J Pharm Sci. 2009:5(2):69-72.
[13] Kaurav H, HariKumar S, Kaur A. Mucoadhesive microspheres as carriers in drug delivery: a review. Int J Drug Dev Res. 2012;4(2):21-34.
[14] Shravani Y, Ahad HA, Haranath C, Gari Poojitha B, Rahamathulla S, Rupasree A. Past Decade Work Done On Cubosomes Using Factorial Design: A Fast Track Information for Researchers. Int J Life Sci Pharma Res. 2021;11(1):124-35.
[15] Balamurugan M, Saravanan V, Ganesh P, Senthil S, Hemalatha P, Pandya S. Development and in-vitro evaluation of mucoadhesive buccal tablets of domperidone. Res J Pharm Technol. 2008;1(4):377-80.
[16] Hussain MM, Nappinai M. Development and method validation of an unconventional in-vitro test to measure mucoadhesive strength of tablets. Res J Pharm Technol. 2009;2(2):363-5.
[17] Ahad HA, Haranath C, Rahul Raghav D, Gowthami M, Naga Jyothi V, Sravanthi P. Overview on Recent Optimization Techniques in Gastro Retentive Microcapsules by Factorial Design. Int J Pharm Sci Res. 2019;10(9):247-54.
[18] Verma M, Bhatnagar S, Kumari K, Mittal N, Sukhralia S, At SG, et al. Highly conserved epitopes of DENV structural and non-structural proteins: Candidates for universal vaccine targets. Gene. 2019;695:18-25.
[19] Jain SK, Awasthi A, Jain N, Agrawal G. Calcium silicate-based microspheres of repaglinide for gastroretentive floating drug delivery: Preparation and in vitro characterization. J Control Release. 2005;107(2):300-9.
[20] Talukder R, Fassihi R. Gastroretentive delivery systems: hollow beads. Drug Dev Ind Pharm. 2004;30(4):405-12.
[21] Liu Y, Zhang J, Gao Y, Zhu J. Preparation and evaluation of glyceryl monooleate-coated hollow-bioadhesive microspheres for gastroretentive drug delivery. Int J Pharm. 2011;413(1-2):103-9.
[22] Garg R, Gupta G. Gastroretentive floating microspheres of silymarin: preparation and in vitro evaluation. Trop J Pharm Res. 2010;9(1):59-66.
[23] Chinthaginjala H, Ahad HA, Samhitharao B, Yasaswini VS, Madana G, Varam NJ, et al. Formulation and in vitro evaluation of fast disintegrating tablets of an anti-inflammatory drug

using natural super disintegrating agents. Int J Life Sci Pharma Res. 2021;11(2):9-18.

[24] Abdul AH, Bala AG, Chintaginjala H, Manchikanti SP, Kamsali AK, Dasari RR. Equator Assessment of Nanoparticles Using the Design-Expert Software. Int J Pharm Sci Nanotechnol. 2020;13(1):4766-72.

[25] Nandare DS, Mandlik SK, Khiste SK, Mohite YD. Formulation and Optimization of Mouth dissolving tablets of Olanzapine by using 32 Factorial Design. Magnesium. 2011;1200:45.

[26] Patel AK, Mishra MK, Gupta J, Ghoshal S, Gupta R, Kushwaha K. Guar Gum-Based Floating Microspheres of Repaglinide Using 32 Factorial Design: Fabrication, Optimization, Characterization, and In Vivo Buoyancy Behavior in Albino Rats. Assay Drug Dev Technol. 2021;19(2):63-74.

[27] Deshmukh MT, Mohite SK. Formulation & characterization of olanzepine-loaded mucoadhesive microspheres. Asian J Pharm Clin Res. 2017;10(4):41-2.

[28] Paul B, Adimoolam S, Javed Qureshi M. Development and Evaluation of Amoxicillin Loaded Carbopol 934P Mucoadhesive Microcapsules for Sustained Drug Release for H. pylori Treatment. Iran J Pharm Sci. 2019;15(3):61-80.

[29] Lal C, Garg R, Gupta GD. Formulation and optimization of mucoadhesive microspheres of valsartan by using box-behnken design. Int J Appl Pharm. 2019;11(4):371-9.

[30] Bhavani J, Saloni S, Rajeshri D. Formulation and evaluation of floating microspheres using factorial design. Int J Recent Sci Res. 2019;10(12):36363-70.

[31] Singh I, Kamboj S, Rana V. Quality by Design Based Fabrication of Iron Oxide Induced Mucoadhesive Microspheres for Enhanced Bioavalibility of Cinnarizine. Curr Drug Deliv. 2017;14(8):1154-69.

[32] Deshmukh MT, Mohite SK. Preparation and evaluation of mucoadhesive microsphere of fluoxetine Hcl. Int J Pharm Sci Res. 2017;8(9):3776-85.

[33] Chilukala S. Formulation Development of Floating Microspheres of Cefditoren Pivoxel by 32 Factorial Design and in Vitro Characterization. Asian J Pharm. 2016;10(1):S14-S22.

[34] Hardenia A, Gupta AK, Singh RP. In Vitro and in Vivo evaluation of mucoadhesive microspheres for treatment of helicobacter pylori using factorial design. J Drug Deliv Ther. 2017;7(7):65-8.

[35] Rai SY, Ravikumar P. Development and evaluation of microsphere based topical formulation using design of experiments. Indian J Pharm Sci. 2016;78(2):182-92.

[36] Thulluru A, Varma MM, Setty CM, Anusha A, Chamundeeswari P, Sanufar S. Formulation, in vitro and in vivo evaluation of pioglitazone hydrochloride–effervescent gastro retentive floating hydrophilic matrix tablets. Int J Pharmtech Res. 2016;9(7):388-98.

[37] Tandel H, Bhatt P, Jain K, Shahiwala A, Misra A. In-vitro and in-vivo tools in emerging drug delivery scenario: Challenges and updates. In-vitro and in-vivo tools in drug delivery research for optimum clinical outcomes. 2018:19-42.

[38] Kumar S, Nanda A. Formulation optimization and in vitro evaluation of gastroretentive mucoadhesive microspheres of Furosemide. Int J Pharm Pharm Sci. 2016;8(7):392-8.

[39] Shah SS. Preparation and evaluation of spray-dried mucoadhesive microspheres for intranasal delivery of prochlorperazine using factorial design. Asian J Pharm (AJP). 2015;9(3):178-89.

[40] Anand N. Nano medicines and Drug Delivery, Research & Reviews. J Pharm Nanotechnol. 2014;4(2):1-6.

[41] Chandiran S, Kumar BP, Narayan V. Formulation and in vitro evaluation of floating drug delivery system for salbutamol sulphate. Int J Pharma Biomed Sci. 2010;1(1):12-5.

[42] Awasthi R. Preparation, characterization and evaluation of ranitidine hydrochloride-loaded mucoadhesive microspheres. Polim Med. 2014;44(2):75-81.

[43] Abedullahh MH. Box-behnken design for development and optimization of acetazolamide microspheres. India. 2014;5(4):1228-39.

[44] Setia A, Kansal S, Goyal N. Development and optimization of enteric coated mucoadhesive microspheres of duloxetine hydrochloride using 32 full factorial design. Int J Pharm Investig. 2013;3(3):141-50.

[45] Nila MV, Sudhir MR, Cinu TA, Aleykutty NA, Jose S. Floating microspheres of carvedilol as gastro retentive drug delivery system: 32 full factorial design and in vitro evaluation. Drug Deliv. 2014;21(2):110-7.

[46] Nappinnai M, Sivaneswari S. Formulation optimization and characterization of gastroretentive cefpodoxime proxetil mucoadhesive microspheres using 32 factorial design. J Pharm Res. 2013;7(4):304-9.

[47] Gandhi S. Optimization of floating microspheres of captopril using full factorial design. Asian J Biomed Pharm Sci. 2012;2(15):69.

[48] Senthil A, Thakkar HR, Dave MV. Design and optimization of mucoadhesive microspheres of

Venlaflaxine HCl using 23 full factorial designs. Pharm Lett. 2011;3(3):202-11.

[49] Natarajan R, Raj GE, Rangapriya M, Rajendran NN. Optimization and evaluation of mucoadhesive microspheres of atenolol. Int J Res Pharm Chem. 2011;1(3):722-9.

[50] Patel DM, Patel MJ, Patel AN, Patel CN. Formulation and evaluation of mixed matrix gastro-retentive drug delivery for famotidine. Int J Pharm Investig. 2011;1(4):247-54.

[51] Dehghan S, Aboofazeli R, Avadi M, Khaksar R. Formulation optimization of nifedipine containing microspheres using factorial design. Afr J Pharm Pharmacol. 2010;4(6):346-54.

[52] Patel J, Patel D, Raval J. Formulation and evaluation of propranolol hydrochloride-loaded carbopol-934p/ethyl cellulose mucoadhesive microspheres. Iran J Pharm Res. 2010;9(3):221-32.

[53] Kharia AA, Hiremath SN, Singhai AK, Omray LK, Jain SK. Design and optimization of floating drug delivery system of acyclovir. Indian J Pharm Sci. 2010;72(5):599-606.

[54] Rao MR, Borate SG, Thanki KC, Ranpise AA, Parikh GN. Development and in vitro evaluation of floating rosiglitazone maleate microspheres. Drug Dev Ind Pharm. 2009;35(7):834-42.