ORIGINAL ARTICLE

The Factorial Design of Experiments to Check Multiple Factors at Once with a Special Focus on Past Efforts in The Optimization of Gastro Retentive Microcapsules

Gorantla Naresh Babu[1], Menaka M[2] and Dr. Hindustan Abdul Ahad[3*]

[1]Research Scholar, Department of Pharmacy, Annamalai University, Annamalai Nagar-608002, Tamil Nadu, India.
[2]Department of Pharmacy, Annamalai University, Annamalai Nagar-608002, Tamil Nadu, India.
[3]M. Pharm., PhD., FAGE, Department of Industrial Pharmacy, Raghavendra Institute of Pharmaceutical Education and Research (RIPER)-Autonomous, Ananthapuramu, Andhra Pradesh, India.

ABSTRACT A current literature review aims to determine whether microcapsules that are gastro-retentive can be made by factorial design for drug delivery. The use of design-of-experiments (DoE) in the optimization of dosage form design is preferred over using trial-and-error in order to eliminate errors and observe the impact of process variables. Software for DoE is easy to use, cheap, and accessible by a simple click of the mouse. In this study, the authors gathered information on all drugs and polymers that have so far been explored in the creation of gastro retentive microspheres, as well as their contributions and the response they produced. A glance is given here at the attempts made so far to create gastro retentive microspheres by using factorial design.

Keywords: Microspheres, Gastro retentive, Design, Variables, Optimization

Address for correspondence: Dr. Hindustan Abdul Ahad, Professor & Head, Department of industrial Pharmacy, Raghavendra Institute of Pharmaceutical Education and Research (RIPER)-Autonomous, KR Palli Cross, Cheyyedu-515721, Ananthapuramu, Andhra Pradesh, India. E-mail: abdulhindustan@gmail.com

Submited: 21-Nov-2021 **Accepted:** 19-Mar-2022 **Published:** 10-Apr-2022

INTRODUCTION

A well-designed experiment can be set up efficiently and effectively under an experimental design. For an untested effort, an appropriate experimental design exploits the quantity of data achievable. Since a few years ago, design of experiments (DoE) techniques have been used in the pharmaceutical arena to optimize processes, familiarizing many researchers with them [1, 2]. In 1967, the first article on comprehensibly using optimization was published when it studied the optimization of sodium salicylate tablets using factorial designs. Even with marvellous improvements in the various ways of taking medicines, oral administration remains the preferred method as it is totally natural, economical, and easier for patients to take. It is fairly common to take extended-release medications orally. An example would be a conventional dosage form followed by a sequence of schemes. DoE's bibliographic literature is largely focused on optimizing polymer levels for rate-sensitive polymers.

Access this article online
Website: www.ijfans.org
DOI: 10.54876/ijfans_57-21

For the scheming of floating microcapsules, the usual independent variables were the polymers (natural/semi-synthetic/synthetic origin) and other excipients. This Table 1 cites numerous approaches to gastro-retentive drug delivery using factorial designs. An experimental statistical design for optimizing experiments was described here [3, 4].

FACTORIAL DESIGN (FD)

Because of the difficulty of applying statistics to many variables at once, traditional research tactics only investigate one variable at a time. Moreover, multiple factors at once fail as they are non-interdependent, producing false results. In multivariate assessment, the DOE has become a vital component. An accord with a fractional number of factors is implied by DOE

How to cite this article: Gorantla Naresh Babu, Menaka M and Dr. Hindustan Abdul Ahad. The Factorial Design of Experiments to Check Multiple Factors at Once with a Special Focus on Past Efforts in The Optimization of Gastro Retentive Microcapsules. Int J Food Nutr Sci 2022; 11(2): 22-36.

[5]. DOE is concerned with response and optimization to broadcasts. An FD identifies every possible incorporation of the factors in the imitation. In FD, each level is designated as "high" (+1) or "low" (-1), and the inputs are all characterized by two levels. An example of a two-level design would be 2, 3, 4, 5, 6, 7 and so forth. There will be 4 numerical runs, 8 numerical runs, 16 numerical runs, 32 numerical runs, 64 numerical runs, etc. In trials with more than five factors, fractional FD or Plackett-Burman design (PBD) must be used. Screening goals for 2-4 factors are flushed and response surface goals are Central composite (CCD) or Box-Behnken (BBD). If 5 factors are present, the screening goal is either FD or PBD, and the screening goal suits the response surface. There are many software optimization tools available, including Design expert (stat-ease), STATISTICA, SPSS, and Minitab, etc. [6]. By entering controllable independent variables, designs were created to produce a controlled outcome. Numerous industrial products or processes have been optimized using experimental designs. Factorial designs are becoming increasingly popular.

DoE Steps

The stages involved in the DOE are explained in Figure 1 [7].

Applications of DOE in Process Development

The applications of DOE in the development of the process are demonstrated in Figure 2 [8, 9].

DOE Targets

DOE has the following goals (Figure 3) [10, 11]:

DOE Applications in Designing

The applications of DOE in design are as follows [12, 13].

- Any additive/antagonistic/synergistic interactions among ingredients
- Identify the key parameters of the design
- A minimal number of trials are required to gather data about a product or process.
- DOE is developing a new formula to achieve controlled dissolution of the drug *in vivo*
- Eliminate or reduce impurities during drug production.
- Equations can be used to simulate the product/process behavior.
- The products' durability.
- Research time spent on inventions, evaluation, and comparison of substitutes is halved.
- A fixed input variable can calculate all response variables in an optimal formulation, so vicissitudes in the formulation can be effortlessly combined.
- It yields the best conceivable formulation.

Figure 1: Various Phases in the DOE

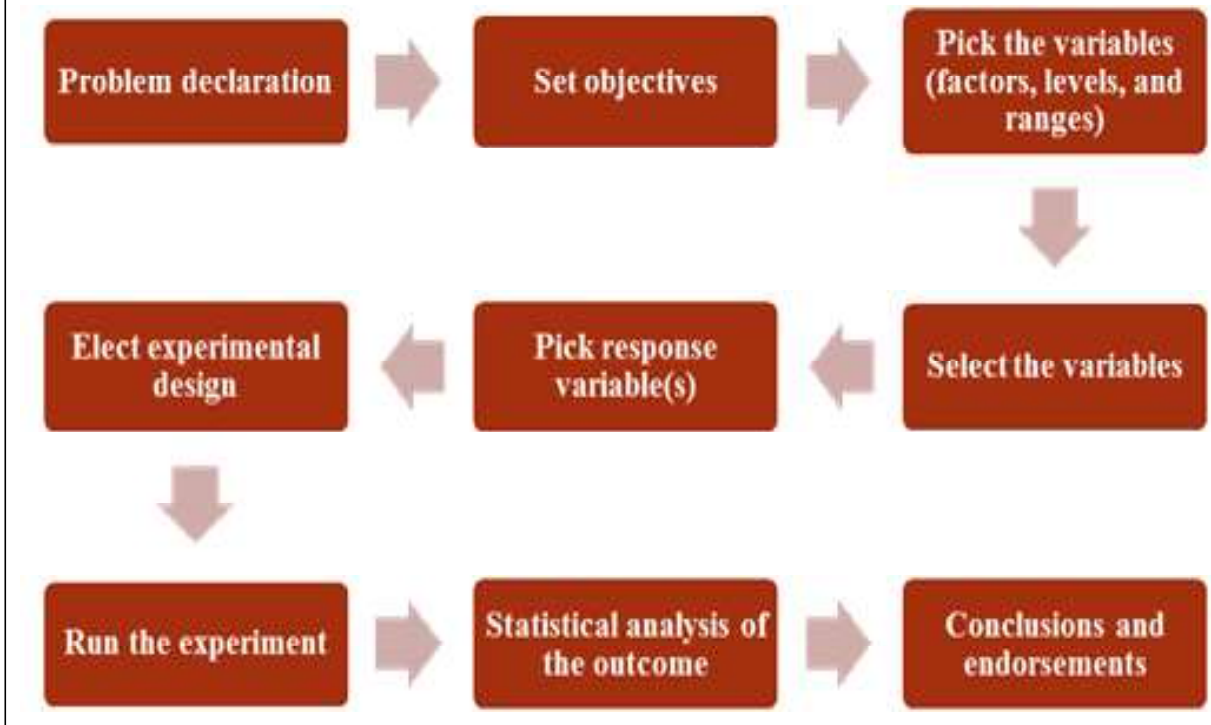


Figure 2: Presentations of DOE on the Progress of a Process

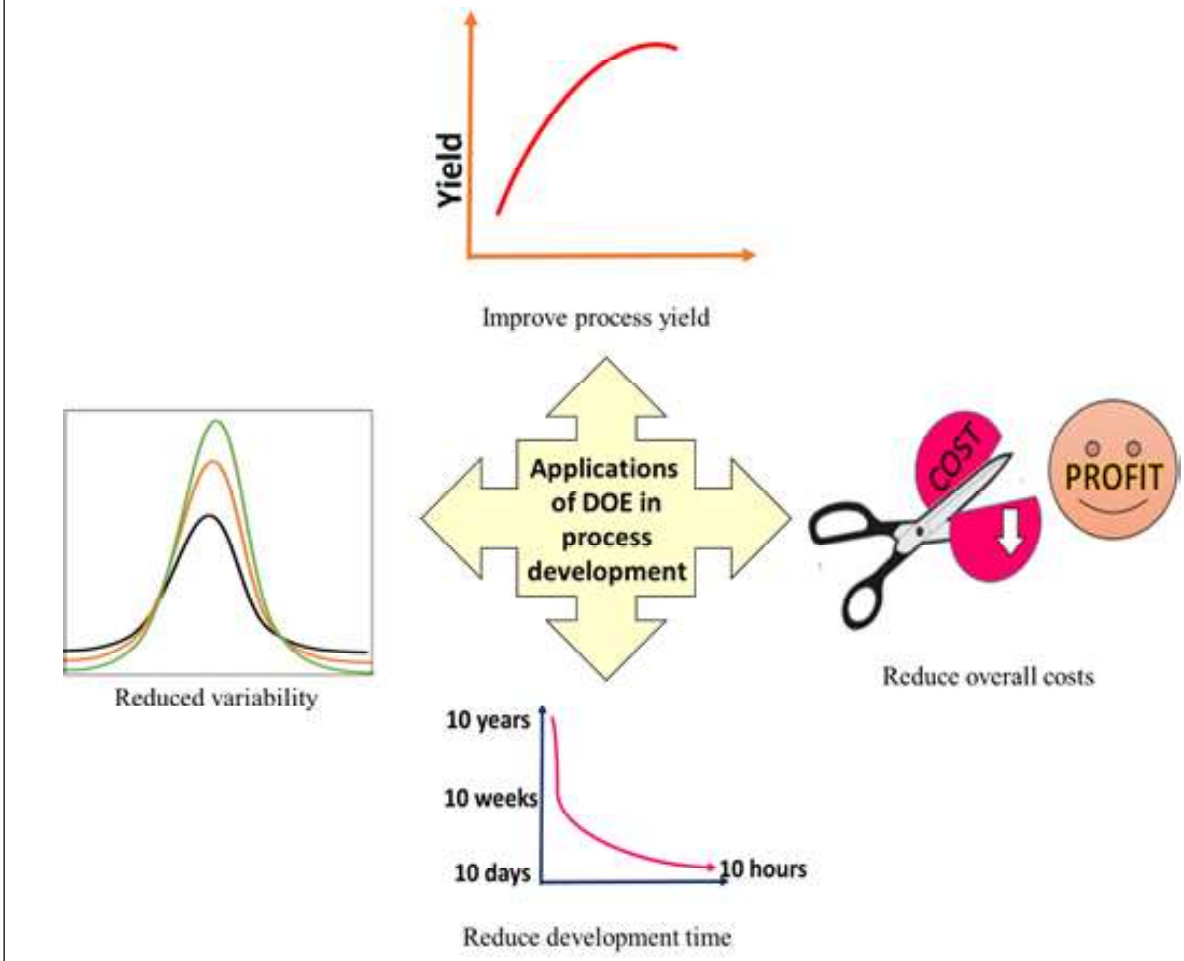
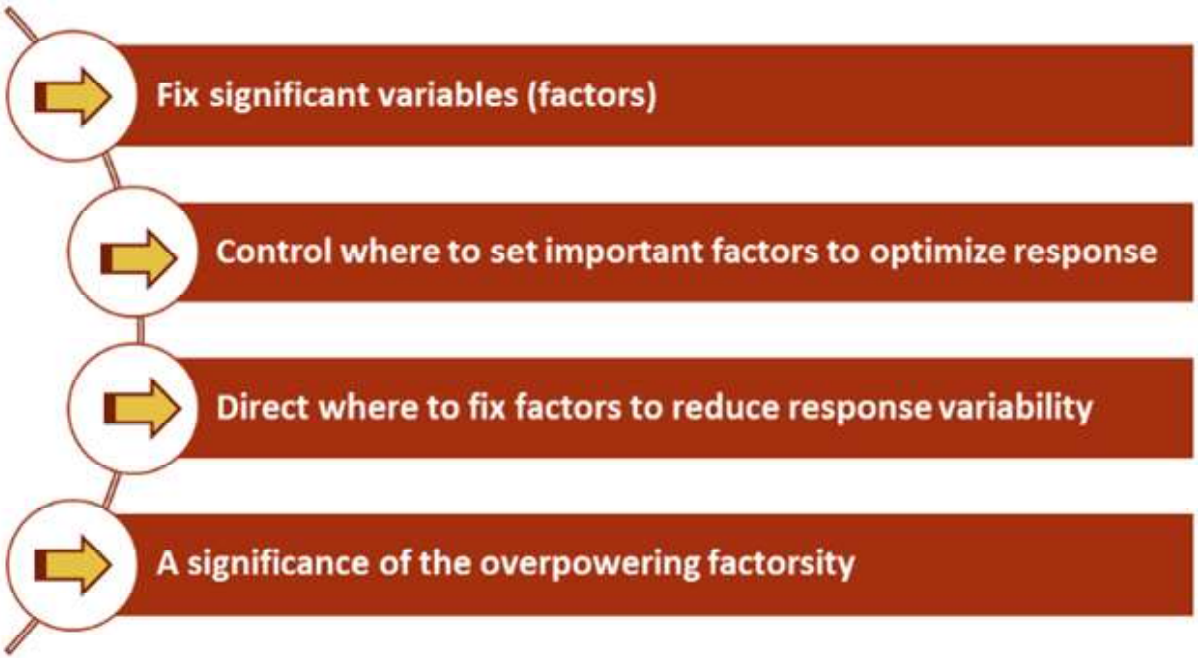


Figure 3: The Goals of DOE



OPTIMIZING ORAL GASTRO RETENTIVE MICROCAPSULES

There is evidence from pharmaceutical journals and texts that the DoE optimization process has been employed for almost all dosage forms. This article describes the DoE optimization practices (factory designs) that have been implemented and successfully used to design gastro retentive microcapsules (Table 1).

Table 1: Earlier Attempts on Gastro Retentive Microcapsules by the Factorial Design

Drug	Polymers	Design	Predictor Variables	Response Variables	Reference
Sitagliptin	Thiolated chitosan	Box–Behnken design (BBD)	Polymer concentration (PC) (X_1)	Particle size (PS), entrapment efficiency (EE), and drug release (DR)	Prabakar *et al.*, 2020 [14]
Acyclovir	Methocel K15M and Ethocel	BBD	PC (X_1), (X_2), and rotations per minute (RPM) (X_3)	DR at 8 h (Y_1), bond strength (BS) (Y_2), and swelling at 4 h (Y_3)	Karmoker *et al.*, 2019 [15]
Carvedilol phosphate	Karaya gum and Carboxymethyl locust bean gum	3^2 full factorial design (FFD)	PC (X_1)	PS (Y_1), EE (Y_2), and DR (Y_3)	Bibek *et al.*, 2019 [16]
Zidovudine	sodium alginate (SA) and uriddall	BBD	PC (X_1)	EE (Y_1), and PS (Y_2)	Gada *et al.*, 2019 [17]
Repaglinide	Methocel K15M, and Eudragit L 100	3^2 FFD	Methocel K15M CR (X_1), Eudragit L 100 (X_2) and rpm (X_3)	DR at 8 h (Y_1), BS (Y_2), and swelling at 8 h (Y_3)	Bhowmick *et al.*, 2019 [18]
Valsartan	Ethyl cellulose (EC), and carbopol 934P	BBD	EC (X_1), carbopol 934P (X_2) and RPM (X_3)	Mucoadhesive strength (MS) (Y_1), DR at Q1h (Y_2), t90% (Y_3) and EE (Y_4)	Lal *et al.*, 2019 [19]
Cefixime Trihydrate	Alginate- chitosan	3^2 FFD	Alginate (X_1), chitosan (X_2)	EE (Y_1), and PS (Y_2)	Sindhumol, 2018 [20]
Metoclopramide HCl	Eudragit S100, L100,RS 100 & RL 100 and EC	3^2 FFD	Eudragit S100 (X_1), Eudragit L100 (X_2), Eudragit RS 100 (X_3), & RL 100 (X_4), and EC (X_5)	EE (Y_1), and PS (Y_2)	Monika *et al.*, 2018 [21]
Lopinavir	Thiolated xyloglucan, Alginate	3^2 FFD	Thiolated xyloglucan (X_1), and Alginate (X_2)	EE, 80% DR (T80) (Y_1), and MS after 1 h (Y_2).	Madgulkar *et al.*, 2018 [22]
Sildenafil citrate	*Azadirachta Indica* (AI) gum	3^2 FFD	AI (X_1)	EE (Y_1), PS (Y_2).	Vijayavani *et al.*, 2018 [23]
Clopidogrel bisulphate	HPMC K15 and Sodium bicarbonate	3^2 FFD	HPMC K15 (X_1)	EE (Y_1), PS (Y_2)	Sanjeevani *et al.*, 2018 [24]
Metronidazole	Carbopol 934P	3^2 FFD	Carbopol 934P (X_1)	EE (Y_1), PS (Y_2)	Bolai, 2018 [25]
Saxagliptin	SA and HPMC K4M.	3^2 FFD	SA (X_1) and HPMC K4M (X_2)	EE (Y_1), PS (Y_2)	Talat *et al.*, 2018 [26]

Table 1 (Cont.)

quetiapine fumarate	EC, HPMC (K4M, K15M & K100M) and Chitosan	2^{5-2} FFD	EC (X_1), HPMC-K4M (X_2), HPMC- K15M (X_3) & HPMC-K100M) (X_4) and Chitosan (X_5)	EE (Y_1), PS (Y_2) and DR (Y_3)	Someshwar *et al.*, 2018 [27]
diclofenac sodium	Tamarind seed gum, hydrolyzed polymethacrylamid e-g-gellan (h-Pmaa-g-GG)	3^2 FFD	Polymer concentration (PC) (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Gouranga *et al.*, 2018 [28]
Ibuprofen	Acetylated plantain starches	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Adenike and Tokoni, 2018 [29]
Lafutidine	HPMC K4M, calcium carbonate and SA	2^3 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Ritesh *et al.*, 2018 [30]
dipyridamole	HPMC K4M, and EC	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Vanshiv *et al.*, 2017 [31]
Repaglinide	*Dioscorea dumetorum* and *Dioscorea oppositifolia*	3^2 FFD	PC (X_1) and X_2	EE (Y_1), PS (Y_2). DR (Y_3)	Adenike *et al.*, 2017 [32]
Losartan potassium	EC	3^2 FFD	EC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Gokul *et al.*, 2017 [33]
Losartan potassium	EC	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Khairnar *et al.*, 2017 [34]
Ranitidine HCl	chitosan, chitosan/HPMC, and chitosan/methylcellulose (MC)	3^2 FFD	PC (X_1, X_2, and X_3)	PS (Y_1), SI (Y_2), EE (Y_3) and MA (y_4)	Khattab *et al.*, 2017 [35]
Amoxicillin	EC, carbopol-934P	3^3 FFD	EC (X_1), carbopol-934P (X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Hardenia and Gupta, 2016 [36]
Carbamazepine	Eudragit RL 100	2^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Nusrat *et al.*, 2016 [37]
Clarithromycin	Pullulan acetate	2^3 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Mishra *et al.*, 2016 [38]
Carvedilol	Carbopol 940, and HPMC	3^2 FFD	Carbopol 940 (X_1) and HPMC (X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Khalid, 2016 [39]
cefditoren pivoxel	HPMC K4M and EC	3^2 FFD	HPMC K4M (X_1) and EC (X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Swathi 2016 [40]
Amoxicillin	Carbopol-934P	3^3 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Anu, 2016 [41]
Diltiazem HCl	SA and HPMC K4M	3^2 FFD	SA (X_1) and HPMC K4M (X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Naresh and Shrikant, 2016 [42]

Table 1 (Cont.)

Ramipril	Sod. CMC, HPMC K4M and Carbopol-934	3^2 FFD	PC (X_1, X_2 and X_3)	EE (Y_1), PS (Y_2). DR (Y_3)	Iftequar, 2016 [43]
Sitagliptin	HPMC K4M and Psyllium husk	3^2 FFD	PC (X_1, and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Sushil *et al.,* 2016 [44]
Carvedilol	SA and sodium CMC	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Sakhare *et al.,* 2016 [45]
Paclitaxel	Acacia, Carbomer 941, hypromellose K-15, methyl cellulose, povidone K-30, PEG 6000, gelatin, SA, chitosan	2^4 FFD	PC (X_1, X_2 , X_3, X_4, X_5, X_6, X_7, X_8, and X_9)	EE (Y_1), PS (Y_2). DR (Y_3)	Chinmaya *et al.,* 2016 [46]
Loratadine	EC, PVA	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Sonam and Kamla, 2016 [47]
Melatonin	Chitosan/Pluronic ® F127	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Marieta *et al.,* 2016 [48]
Acyclovir	SA and Gelatin	3^2 FFD	PC (X_1 and X_2)	Viscosity (Y_1), gel strength (Y_2), the onset of floatation (Y_3), and DR (Y_4)	Singh *et al.,* 2016 [49]
Ibuprofen	Poly (ε-caprolactone), and poly(ethylene glycol)–poly(ε-caprolactone) copolymer	2^4 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Azouz *et al.,* 2016 [50]
Ketoprofen	EC and Eudragit RL 100	3^3 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Sanjoy *et al.,* 2016 [51]
Diltiazem HCl	Polycarbonate	2^3 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Panwar *et al.,* 2015 [52]
Carvedilol	HPMCK100M	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Gunda *et al.,* 2015 [53]
Prochlorperazine	EC	2^3 FFD	feed flow rate (X_1) and volume of gluteraldehyde (X_2)	PS, and EE	Shah *et al.,* 2015 [54]
Ranitidine HCl	HPMC K100M and Carbopol 971	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Jabbar, 2015 [55]
Fluconazole	β-cyclodextrin, HPMC, hydroxyethyl	2^3 FFD	PC (X_1 and X_2, X_3 and X_4)	Hardness (Y_1), SI (Y_2), and DR (Y_3)	Hani *et al.,* 2015 [56]
Captopril	Xanthan gum and HPMC K100M	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Ahsan, 2015 [57]
Tenofovir	Eudragit RS PO	BBD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2)	Matlhola *et al.,* 2015 [58]

Table 1 (Cont.)

Propranolol HCl	EC	3^3 FFD	PC (X_1), RPM (X_2) and proportion of dispersion medium (X_3)	PS (Y_1), %yield (Y_2), buoyancy (BA) (Y_3), drug content (Y_4), EE (Y_5), and DR (Y_6)	Joshi *et al.*, 2015[59]
Prazosin HCl	HPMC K100	2^3 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Vanitha, 2015 [60]
Zolpidem Tartarate	EC and HPMC 5 cps	2^3 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Sachin, 2015[61]
Carvedilol	EC and HPMC	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Nila *et al.*, 2014[62]
Gabapentin	SA and sodium CMC	BBD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Gaur *et al.*, 2014 [63]
Acyclovir	EC and Carbopol 940	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Kyada *et al.*, 2014 [64]
Cefpodoxime Proxetil	Eudragit S100	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Monica, 2014 [65]
Ramipril	Eudragit E100, and Glycerol monostearate	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Tushar *et al.*, 2014 [66]
Glipizide	HPMCK4M and Carbopol934	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Sujata *et al.*, 2014 [67]
Cefdinir	Gum Karaya	2^3 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Sarath and Suresh, 2014 [68]
Ziprasidone HCl	EC and PVP	2^3 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Praneeth *et al.*, 2014 [69]
Pioglitazone	HPMC K100 and Carbopol 934	3^3 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Wattamwar *et al.*, 2014 [70]
Clopidogrel bisulphate	Xanthan gum, HPMC K15M, and HPMC K4M	2^3 FFD	PC (X_1, X_2) and X_3)	EE (Y_1), PS (Y_2). DR (Y_3)	Bhadouriya et al. 2013 [71]
Acyclovir	HPMC K15M and polyethylene oxide (PEO)	3^2 FFD	PEO (X1) and HPMC K15M (X2)	DR at 3h-Q_3 (Y1), 9h-Q_9 (Y2) and 12 h-Q_{12} (Y_3)	Shahi *et al.*, 2013 [72]
Verapamil HCl	HPMC K4M	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Shahi et al. 2013 [73]
Duloxetine HCl	Eudragit L-100	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Anupama, 2013 [74]
Cefpodoxime proxetil	Chitosan	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Nappinnai and Sivaneswari, 2013 [75]
Agrochemical 2,4-D	EC, HPMC, cellulose acetate butyrate	2^2 FFD	PC (X_1, X_2) and X_3)	EE (Y_1), PS (Y_2). DR (Y_3)	Fatima *et al.*, 2013 [76]

Table 1 (Cont.)

Captopril	HPMC K4M, EC and SA	3^2 FFD	PC (X_1, X_2) and X_3)	EE (Y_1), PS (Y_2). DR (Y_3)	Durgavale et al. 2012 [77]
Captopril	Eudragit RL-100 and EC	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Sanket, 2012 [78]
Ranitidine HCl	Eudragit RL-100.	2^3 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Jhansipriy, 2012 [79]
Captopril	HPMC K4M	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Devesh, 2012 [80]
Ciprofloxacin HCl	EC and HPMC 5 cps	2^3 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Narendra *et al.*, 2012 [81]
Tolperisone	EC and HPMC 15 cps	2^3 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Pooja *et al.*, 2012 [82]
Celecoxib	Eudragit L-100 and PVP	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Shahzad *et al.*, 2012 [83]
Acyclovir	HPMC 4000, Compritol 888.	3^2 FFD	HPMC4000 (X_1) and Compritol 888 (X_2)	DR in 1h-Q_1 (Y_1), 6h-Q_6 (Y_2), and 12h-Q_{12} (Y_3)	El Gamal *et al.*, 2011 [84]
Cephalexin	EC and PVA	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Kamini and Rajesh, 2011 [85]
Acyclovir	EC	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Parmar, 2011 [86]
Acyclovir	Poly (lactic-co-glycolic acid) (PLGA), and polycarbophil	2^3 FFD	PC (X_1, and X_2)	PS (Y_1), EE (Y_2) and DR in 12 h (Y_3)	Bhosale *et al.*, 2011 [87]
Metformin HCl	EC, HPMC and SA	3^2 FFD	PC (X_1, X_2 and X_3)	EE (Y_1), PS (Y_2). DR (Y_3)	Masa *et al.*, 2011 [88]
Risedronate sodium	PLGA	2^4 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Maha *et al.*, 2011 [89]
Stavudine	EC	3^2 FFD	PC (X_1) and RPM (X_2)	EE (Y_1), EE (Y_2), PS (Y_3) and DR-t_{80} (Y_4)	Sanjay *et al.*, 2011 [90]
Venlafaxine HCl	EC, Eudragit RS100 and HPMC K4M	2^3 FFD	PC (X_1, X_2 and X_3)	DR-t_{80} (Y_1), MS (Y_2)	Senthil *et al.*, 2011 [91]
Pioglitazone HCl	EC and HPMC K100M	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Satish, 2010 [92]
Acyclovir	psyllium husk and HPMC K4M	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Kharia *et al.*, 2010 [93]
Bovine serum albumin	Chitosan and Alginate	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Sevgi and Aybige, 2010 [94]
Metformin	SA and Gellan gum	3^3 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Nagarwal *et al.*, 2009 [95]

Table 1 (Cont.)

Clarithromycin	HPMC 15M, HPMC K4M, HPMC 100LV and EC.	3^2 FFD	PC (X_1 and X_2, X_3 and X_4)	EE (Y_1), PS (Y_2). DR (Y_3)	Chudiwal *et al.*, 2009 [96]
Metformin	SA and gellan gum	3^3 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Ramesh, 2009 [97]
Glipizide	Polycarbophil and SA	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Hosmani *et al.*, 2009 [98]
Glipizide	SA, carbapol 974P and SCMC	2^3 FFD	PC (X_1 and X_2 and X_3)	EE (Y_1), PS (Y_2). DR (Y_3)	Sanap, 2009 [99]
Clarithromycin	carbopol 934 P & polycarbophil	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Yogesh *et al.*, 2009 [100]
Clarithromycin	HPMC K4M	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Shahi, 2008 [101]
Tretinoin	cellulose acetate, PVA	2^3 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Tabbakhian *et al.*, 2008 [102]
Cinnarizine	Eudragit S100, Eudragit RL,	3^2 FFD	PC (X_1 and X_2)	EE (Y_1), PS (Y_2). DR (Y_3)	Varshosaz *et al.*, 2007 [103]
Glipizide	Chitosan	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Jayvadan *et al.*, 2005 [104]
Acyclovir	Poly (d,l-lactide-co-glycolide)	2^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Martinez *et al.*, 2004 [105]
Propranolol	HPMC K4M, K100LV and Carbopol P934	2^3 FFD	PC (X_1 and X_2, and X_3)	EE (Y_1), PS (Y_2). DR (Y_3)	Li, *et al.*, 2003 [106]
5-fluorouracil	Poly (D, L-Lactide-Co-Glycolide)	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Rajesh *et al.*, 2003 [107]
Flurbiprofen	Cetyl alcohol	3^2 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Anant *et al.*, 2003 [108]
Diclofenac sodium	SA	3^3 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Gohel and Amin, 1998 [109]
Salbutamol sulphate	Poly (lactic acid-co-glycolic and PVA	2^3 FFD	PC (X_1)	EE (Y_1), PS (Y_2). DR (Y_3)	Nevin *et al.*, 1996 [110]

CONCLUSION

Earlier, one factor at a time was a trial-and-error procedure that took time when multiple experiments were planned. Multi-factor checks lead to many errors. To avoid errors and to understand the impact of independent variables on the output, these DoE methods are more often applied. Researchers will be able to use the information collected on experiments to microsphere gastro-retentive dosage forms using QbD optimization in the future to carry out experiments and to determine the impact of variables on results. DoE is being adopted as an industry standard due to its ease, accuracy, and affordability. It can be implemented with one click of the mouse. Researchers will find the article helpful if they want to optimize gastro-retentive microspheres quickly by working on DOE.

ACKNOWLEDGMENT

The authors were thankful to the college management for encouragement and support.

REFERENCES

1. Telford JK. (2007). A brief introduction to design of experiments. Johns Hopkins apl technical digest. Sep; 27(3): 224-32.
2. Anderson MJ, Whitcomb PJ. (2000). Design of experiments. Kirk Othmer Encyclopedia of Chemical Technology. Dec 4: 1-22.
3. Jose N, Sengupta S, Basu JK. (2011). Optimization of oxidative desulfurization of thiophene using Cu/titanium silicate-1 by box-behnken design. Fuel. Feb 1; 90(2): 626-32.
4. Ahad HA, Haranath C, Rahul Raghav D, Gowthami M, Naga Jyothi V, Sravanthi P. (2019). Overview on Recent Optimization Techniques in Gastro Retentive Microcapsules by Factorial Design. Int J Pharm Sci Res. 10(9): 247-54.
5. Anusha GB, Ahad HA, Haranath C. (2019). A technical view on transporters-the drug pharmacokinetics dictators. MOJ Bioequiv Availab. 6(2): 39-45.
6. Chinthaginjala H, Ahad HA, Bhargav E, Pradeepkumar B. (2021). Central Composite Design Aided Formulation Development and Optimization of Clarythromycin Extended-Release Tablets. Indian Journal of Pharmaceutical Education and Research. Apr 1; 55(2): 395-406.
7. Shravani Y, Ahad HA, Haranath C, Gari Poojitha B, Rahamathulla S, Rupasree A. (2021). Past Decade Work Done On Cubosomes Using Factorial Design: A Fast Track Information for Researchers. Int. J. Life Sci. Pharma Res.; 11(1): P124-135.
8. Röpke K, Von Essen C. (2008). DoE in engine development. Quality and Reliability Engineering International. Oct; 24(6): 643-51.
9. Lawrence XY. (2008). Pharmaceutical quality by design: product and process development, understanding, and control. Pharmaceutical research. Apr; 25(4): 781-91.
10. Lee SJ, Bae YS. (2014). Can metal–organic frameworks attain new DOE targets for on-board methane storage by increasing methane heat of adsorption. The Journal of Physical Chemistry C. Aug 28; 118(34): 19833-41.
11. Garland N, Benjamin T, Kopasz J. (2007). DOE fuel cell program: Durability technical targets and testing protocols. ECS Transactions. Sep 28; 11(1): 923.
12. Fricke J, Pohlmann K, Jonescheit NA, Ellert A, Joksch B, Luttmann R. (2013). Designing a fully automated multi bioreactor plant for fast DoE optimization of pharmaceutical protein production. Biotechnology Journal. Jun; 8(6): 738-47.
13. Fukuda IM, Pinto CF, Moreira CD, Saviano AM, Lourenço FR. (2018). Design of experiments (DoE) applied to pharmaceutical and analytical quality by design (QbD). Brazilian Journal of Pharmaceutical Sciences. 54(SPE).
14. Prabahar K, Udhumansha U, Qushawy M. (2020). Optimization of thiolated chitosan nanoparticles for the enhancement of in vivo hypoglycemic efficacy of sitagliptin in streptozotocin-induced diabetic rats. Pharmaceutics. Apr; 12(4): 300.
15. Karmoker JR, Hasan I, Ahmed N, Saifuddin M, Reza MS. (2019). Development and Optimization of Acyclovir Loaded Mucoadhesive Microspheres by Box–Behnken Design. Dhaka University Journal of Pharmaceutical Sciences. May 16; 18(1): 1-2.
16. Bibek L, Rimpa G, Sabyasachi M and Kalyan KS. (2019). Smart karaya-locust bean gum hydrogel particles for the treatment of hypertension: Optimization by factorial design and pre-clinical evaluation, Carbohydrate Polymers, 210: 274-288.
17. Gada SG, Anandkumar Y, Setty CM. (2019). Design and optimization of zidovudine loaded uriddall mucilage microspheres, using box behnken method. International Journal of Pharmaceutical Sciences and Research. Vol. 10(4): 1856-1864.
18. Bhowmick A, Saha T, Karmoker JR, Reza MS. (2019). Design of experiment (doe) approach to prepare, characterize and optimize the gastroretentive mucoadhesive microspheres of repaglinide. Bangladesh Pharmaceutical Journal. Jul 21; 22(2): 135-45.
19. Lal C, Garg R, Gupta Gd. (2019). Formulation and Optimization of Mucoadhesive Microspheres of Valsartan by Using Box-Behnken Design. International Journal of Applied Pharmaceutics. Jul 7: 371-9.
20. Sindhumol PG, Sudhakaran CR. (2018). Formulation and Optimization of Floating Microcapsules of Cefixime Trihydrate by Factorial Design, Int. J for Pharm Res. Scholars, 7 (1):
21. Monika KD, Pournima MH, Manisha KS and Vilasroa K. (2018). Development and characterization of gastro retentive floating microsphere for controlled release of metoclopramide hydrochloride, Indian J of Drugs, 6(4): 189-200.

22. Madgulkar AR, Bhalekar MR, Kadam AA. (2018). Improvement of oral bioavailability of lopinavir without co-administration of ritonavir using microspheres of thiolated xyloglucan. AAPS Pharm Sci Tech. Jan; 19(1): 293-302.

23. Vijayavani SC, Vidyavathi M. (2018). Azadirachita indica gum based sildenafil citrate mucoadhesive microspheres–Design and optimization. Journal of Drug Delivery Science and Technology. Oct 1; 47: 499-513.

24. Sanjeevani SD, Arvind SP and Satish VS. (2018). Formulation and optimization of floating tablets of clopidogrel bisulphate using design of experiments, Int. J App Pharm, 10(6): 94-102.

25. Bolai P, Senthil A, Mohd JQ. (2018). Development and evaluation of metronidazole loaded carbopol 934P mucoadhesive microcapsules for sustained drug release at the gastric mucosa, J of Applied Pharm Sci., 8(12): 020-031.

26. Talat F, Azmat S and Sadhana S. (2018). Formulation development of mucoadhesive Microcapsules of antidiabetic drug, World J of Pharm Res., 7(1): 1549-1561.

27. Someshwar K, Suryakanta S, Muddana EBR, Bikash RJ, Sambamoorthy U and Vishali D. (2018). QbD-based design and characterization of mucoadhesive microcapsules ofquetiapine fumarate with improved oral bioavailability and brainbiodistribution potential, Bulletin of Faculty of Pharmacy, Cairo University, 56: 129-145.

28. Gouranga N, Amit KN, Najim SK, Souvik P and Sibasish D. (2018). Tamarind seed gum-hydrolyzed polymethacrylamide-g–gellan beads for extended release of diclofenac sodium using 32 full factorial design, International Journal of Biological Macromolecules, 114: 214-225.

29. Adenike O and Tokoni G. (2018). Development of ibuprofen microcapsules using acetylated plantain starches as polymer for sustained release, J. Pharm. Investig, 48: 551-564.

30. Ritesh K, Pawan KG and Amrish C. (2018). Formulation and Evaluation of Multiple Unit Floating Beads of Antiulcer Drug, Asian Journal of Pharmaceutics, 12(2): S680-S690.

31. Vanshiv SD, Joshi HP and Aware AB. (2018). Formulation and Development of Gastroretentive Dipyridamole Microcapsules: Proof of Concept by in vitro-In vivo Assessment. Indian J Pharm Sci., 80(1): 181-191

32. Adenike O, Amusa SA and Moji CA. (2017). Development of repaglinide microcapsules using novel acetylated starches of bitter and Chinese yams as polymers, International Journal of Biological Macromolecules, 94(A): 544-553.

33. Gokul K, Jitendra N and Vinod M. (2017). A statistical study on the development of micro particulate sustained drug delivery system for Losartan potassium by 3^2 factorial design approach, Bulletin of Faculty of Pharmacy, Cairo University, 55(1): 19-29.

34. Khairnar G, Naik J, Mokale V. (2017). A statistical study on the development of micro particulate sustained drug delivery system for Losartan potassium by 32 factorial design approach. Bulletin of Faculty of Pharmacy, Cairo University. Jun 1; 55(1): 19-29.

35. Khattab A, Zaki N. (2017). Optimization and evaluation of gastroretentive ranitidine HCl microspheres by using factorial design with improved bioavailability and mucosal integrity in ulcer model. AAPS PharmSciTech. May; 18(4): 957-73.

36. Hardenia A and Gupta AK. (2016). Development and Optimization of Gastroretentive Mucoadhesive Microcapsules Using 3^3 Factorial Design. Int J Pharm Sci Res; 7(5): 2020-30.

37. Nusrat A, Ikramul H, Mohammad S, Jakir AC and Selim R. (2016). Formulation and Optimization of Carbamazepine Microcapsules by 2 Factor 2 Level Central Composite Design, Bangladesh Pharm J, 19(2): 152-160.

38. Mishra B, Harthik RK, Manikanta A, Anand A and Sharath KRM. (2016). Formulation and Optimization of Clarithromycin Loaded with Pullulan Acetate Microsphere for Sustained Release by Response Surface Methodology, Int. J Drug Dev. & Res; 8(3): 11-15.

39. Khalid ES. (2016). Optimized gastroretentive floating carvedilol tablets: an approach for prolonged gastric residence time and enhanced absorption, Journal of Applied Pharmaceutical Science, 6(6): 12-19.

40. Swathi C, Vijaya KB, Rajeswara RP. (2016). Formulation Development of Floating Microcapsules of Cefditoren Pivoxel by 3^2 Factorial Design and in Vitro Characterization, Asian J of Pharmaceutics, 9(5): S14.

41. Anu H and Arun KG. (2016). Development and Optimization of Gastro retentive Mucoadhesive Microcapsules Using 33 Factorial Design, I JPSR, 7(5): 2020-2030.

42. Nishan NB and Shrikant DP. (2016). Formulation and Evaluation of Controlled Release Gastro-Retentive in

situ Gel for Diltiazem Hydrochloride, Indian J of Pharm Education and Res., 50(3).

43. Iftequar S, Maria S, Lahoti S, Zahid Z, Sabina M and Furqan K *et al.* (2016). Formulation and evaluation of floating drug delivery system of Ramipril, J of Innovations in Pharm and Bio Sci., 3(1): 85-95.

44. Sushil KS, Ajay T and Shrivastava B. (2016). Formulation Optimization and In-Vivo evaluation of Floating Gastroretentive Microsphere of Sitagliptin by 3^2 Factorial Design. Int. J. Pharm. Sci. Rev. Res., 40(2): 198-206.

45. Sakhared SS, Yadav AV and Jadhav PD. (2016). Design, development and characterization of mucoadhesive gastro spheres of Carvedilol, International Journal of Applied Pharmaceutics, 8(3): 37-42.

46. Chinmaya M, Padala NM, Prasanna KD, Sudhir KS, Anjan KM and Monalisa D. (2016). Statistical Approach in Designing, Formulation and Optimization of Paclitaxel Loaded Mucoadhesive Microcapsules Int. J of Innovative Res. Sci. Eng. and Tech, 5(12): 21331-21339.

47. Sonam S and Kamla P. (2016). Assessing the bioadhesivity of Acconon MC 8-2 EP/NF for gastroretention of floating microsponges of Loratadine and achieving controlled drug delivery, Pharm Biomed Res, 2(2): 58-74.

48. Marieta DR, Maja SK, Jasmina L, Ivan P, Biserka CC, Jele FG, Anita H. (2016). Melatonin-loaded chitosan/ Pluronic F127 microcapsules as in situ forming hydrogel: An innovative antimicrobial wound dressing, European J of Pharmaceutics and Biopharmaceutics, 107: 67-79.

49. Singh B, Kaur A, Dhiman S, Garg B, Khurana RK, Beg S. (2016). QbD-enabled development of novel stimuli-responsive gastroretentive systems of acyclovir for improved patient compliance and biopharmaceutical performance. Aaps Pharmscitech. Apr; 17(2): 454-65.

50. Azouz L, Farid D, Farouk R and Christian G. (2016). Full factorial design optimization of anti-inflammatory drug release by PCL–PEG–PCL microcapsules, Materials Science and Engineering: C, 58(1): 412-419.

51. Sanjoy KD, Jasmina K and Arunabha N. (2016). Optimization of preparation method for ketoprofen-loaded microcapsules consisting polymeric blends using simplex lattice mixture design, Materials Sci. and Eng., C, 69(1): 598-608.

52. Panwar MM. (2015). Factorial design approach for optimization of floating microspheres of diltiazem hydrochloride. Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm. Jul 21; 9(3): 206-12.

53. Gunda RK, Kumar JS, Satyanarayana V, Rani GS, Venkateswarlu G. (2015). Formulation Design, Optimization and Evaluation of Carvedilol Phosphate Gastro Retentive Floating Tablets. Current Research in Pharmaceutical Sciences. Dec 30: 124-35.

54. Shah SS. (2015). Preparation and evaluation of spray-dried mucoadhesive microspheres for intranasal delivery of prochlorperazine using factorial design. Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm. Jul 15; 9(3): 178-89.

55. Jabbar HN, Badreldin SM, Aldawsari HM. (2015). Gastroretentive Ranitidine Hydrochloride Tablets with Combined Floating and Bioadhesive Properties: Factorial Design Analysis, In Vitro Evaluation and in Vivo Abdominal X-Ray Imaging. Curr Drug Deliv.; 12(5): 578-90.

56. Hani U, Shivakumar HG, Srivastava A, Mahammed N, Thirumaleshwar S, kumar Varma NS, Vaghela R, Shinde CG, Gowrav MP. (2015). Design and Optimization of Curcumin–HPâCD Bioadhesive Vaginal Tablets by 2 3 Factorial Design: In Vitro and in Vivo Evaluation. Journal of Pharmaceutical Innovation. Mar 1; 10(1): 21-35.

57. Ahsan M, Nasir A, Amjad H, Hamid S, Pervaiz AS and Sohail M. (2015). Formulation Optimization and In-vitro Evaluation of Oral Floating Captopril Matrix Tablets using Factorial Design, Tropical J of Pharm Res., 14(10): 1737-1748.

58. Matlhola K, Katata-Seru L, Tshweu L, Bahadur I, Makgatho G, Balogun M. (2015). Formulation and optimization of Eudragit RS PO-tenofovir nanocarriers using Box-Behnken experimental design. Journal of Nanomaterials. Jan 1.

59. Joshi A, Chauhan S, Seth A, Shah N, Aundhia C, Javia A. (2015). Influence of Formulation Variable in Development of Floating Microspheres of Water Soluble Drug. Pharma Science Monitor. Jul-Sep; 6(3): 29-40.

60. Vanitha K and Ramesh A. (2015). Optimization and Evaluation of Prazosin Hydrochloride Floating Microcapsules Using Response Surface Methodology, J of Pharm and Bio Sci., 10(3): 58-68.

61. Sachin SP, Rajendra VVS, Beduin M, Vinay R. (2015). Formulation and Evaluation of Floating Microcapsules of Zolpidem Tartarate, Journal of Pharmacy and Biological Sciences, 10(4): 26-38.

62. Nila MV, Sudhir MR, Cinu TA, Aleykutty NA and Jose S. (2014). Floating microcapsules of carvedilol as gastro

retentive drug delivery system: 3^2 full factorial design and in vitro evaluation, Drug Delivery, 21(2): 110-117.

63. Gaur PK, Mishra S, Kumar A, Panda BP. (2014). Development and optimization of gastroretentive mucoadhesive microspheres of gabapentin by Box–Behnken design. Artificial cells, nanomedicine, and biotechnology. Jun 1; 42(3): 167-77.
64. Kyada CK and Ranch DS. (2014). Optimization of Mucoadhesive Microcapsules of Acyclovir by Applying 3^2 Full Factorial Design, Journal of Drug Delivery Science and Technology, 24(1): 61-68.
65. Monica RP, Aafaque Y and Swapnil S. (2014). Formulation and Evaluation of Floating Microcapsules of Cefpodoxime Proxetil, Indian J Pharm Education and Res.; 48(4); 100-108.
66. Tushar P and Bhakti B. (2014). Statistical optimization and in-vitro evaluation of hollow Microcapsules of an anti-hypertensive agent, Acta Poloniae Pharmaceutica ñ Drug Research, 71(1): 95-106.
67. Sujata A, Sradhanjali P, Nihar RP. (2014). Optimization of HPMC and carbopol concentrations in non-effervescent floating tablet through factorial design, Carbohydrate Polymers, 102: 360-368.
68. Sarath C and Suresh KP. (2014). Formulation and evaluation of floating microcapsules of Cefdinir, J of Pharmacy Research, 8(2): 212-216.
69. Praneeth KT, Ramu M, Arun KT, Anil KG, Upender M, Keerthivardhan D. (2014). Development and optimization of floating microballons for hydrodynamic delivery of Ziprasidone Hydrochloride, Int. J of Innovative Pharm Sci. and Res. 2(8): 1765-1782.
70. Wattamwar MM, Ratnaparkhi MP, Kutmalge MD, Jadhav AN. (2014). Formulation and in vitro evaluation of mucoadhesive microcapsules of pioglitazone Hydrochloride, Asian Pac. J. Health Sci., 1(3): 177-192.
71. Bhadouriya P, Kumar M and Pathak K. (2013). Formulation and in vitro evaluation of prolonged release floating microcapsules of atenolol using multi compartment dissolution apparatus. Drug Development and Industrial Pharmacy. 39(11): 1663-1671.
72. Shahi S, Sonawane A, Vanamore S, Zadbuke N. (2013). Formulation and in-vitro characterization of acyclovir floating matrix tablets: a factorial design study. Journal of Applied Pharmaceutical Science. May 1; 3(5): 65.
73. Shahi SR, Shinde SB, Zadbuke NS, PadalkarAN. (2013). Formulation developement and evaluation of floating matrix tablet of Verapamil HCl. Asian J Pharm; 7: 27-35.
74. Anupama S, Sahil K and Naveen G. (2013). Development and optimization of enteric coated mucoadhesive microcapsules of duloxetine hydrochloride using 32 full factorial design, Int J Pharm Investig.; 3(3): 141-150.
75. Nappinnai M and Sivaneswari S. (2013). Formulation optimization and characterization of gastroretentive cefpodoxime proxetil mucoadhesive microcapsules using 32 factorial design, J of Pharmacy Res., 7(4): 304-309.
76. Fatima ZB, Zineb E and Mohamed E. (2018). Preparation and Optimization of Agrochemical 2,4-D Controlled Release Microparticles using Designs of Experiments, J. Mex. Chem. Soc.; 62(1): 1-21.
77. Durgavale AA, Dhole AR, Mohite SK, Magdum CS. (2012). Formulation and Evaluation of Floating Microsphere of Captopril using Different Gas Forming Agents. American Journal of PharmTech Research. 2(2): 565-575.
78. Sanket G, Anil B, Girish KJ, Nishant U and Rucha P. (2012). Optimization of Floating Microcapsules of Captopril Using Full Factorial Design, Asian Journal of Biomedical and Pharmaceutical Sciences, 2(15): 69-94.
79. Jhansipriya MV, Deveswaran R, Bharath S, Basavaraj BV, Madhavan V. (2012). Design and Optimization of Multiparticulate Gastroretentive Delivery System of Ranitidine Hydrochloride, Int J Pharm Pharm Sci, 4(2): 597-603.
80. Devesh K and Rakesh P. (2012). Formulation, Optimization and Evaluation of Floating Microcapsules of Captopril, Asian Journal of Biomedical and Pharmaceutical Sciences, 2(9): 1-10.
81. Narendra B, Prathap M, Venkateswara PR, Sudhakar AM, Ananda CH. (2012). Development and optimization of ciprofloxacin hcl hollow microcapsules (micro ballons) by using factorial design, International Journal of Research in Pharmaceutical and Nano Sciences. 1(2): 202-218.
82. Pooja J, Paresh M, Kantilal V, Hiral B and Ronak D. (2012). Formulation and evaluation of controlled release floating microcapsules of Tolperisone hydrochloride, Asian J Pharm, 6, 190-197.
83. Shahzad MK, Ubaid M and Murtaza G. (2012). Formulation and Optimization of Celecoxib-Loaded Microcapsules Using Response Surface Methodology, Tropical Journal of Pharmaceutical Research October; 11(5): 695-702.
84. El Gamal SS, Naggar VF, Allam AN. (2011). Optimization of acyclovir oral tablets based on

gastroretention technology: factorial design analysis and physicochemical characterization studies. Drug development and industrial pharmacy. Jul 1; 37(7): 855-67.

85. Kamini V, Rajesh KS and Lalit LJ. (2011). Formulation and evaluation of floating microcapsules of cephalexin, 11(2).

86. Parmar KV, Gohel MC, Parikh RK, Shital B, Rajeshvari NS. (2011). Sustained Release Floating Microcapsules of Acyclovir: Formulation, Optimization, and Characterization and in Vitro Evaluation, Int. J Drug Dev. & Res., 3(1): 242-251.

87. Bhosale UV, Kusum Devi V and Jain N. (2011). Formulation and Optimization of Mucoadhesive Nanodrug Delivery System of Acyclovir, Journal of Young Pharmacists, 3(4): 275-283.

88. Masa Reddy RS, Bolmal UB, Patil BR and Shah V. (2011). Metformin Hcl Loaded Sodium Alginate Floating Microcapsules Prepared by Ionotropic Gelation Technique: Formulation, Evaluation and Optimization, Indian J of Novel Drug delivery, 3(2): 125-133.

89. Maha N, Gehanne ASA, Samar M, Abdelhamid AS and Nahed DM. (2011). A Reliable Predictive Factorial Model for Entrapment Optimization of a Sodium Bisphosphonate into Biodegradable Microcapsules, Journal of Pharmaceutical Sciences, 100(2): 612-621.

90. Sanjay D, Soumen P and Ananya M. (2011). Formulation and Optimization of Sustained Release Stavudine microcapsules Using Response Surface Methodology, ISRN Pharmaceutics, 1-7.

91. Senthil A, Thakkar HR, Dave MV. (2011). Design and optimization of mucoadhesive microspheres of Venlaflaxine HCl using 23 full factorial designs. Der Pharmacia Lettre. 3(3): 202-11.

92. Satish VS, Mukund GT, Nishant SG and Nilesh BD. (2010). Development and evaluation of floating microcapsules of Pioglitazone hydrochloride using ethyl cellulose, Der Pharmacia Lettre, 2(5): 261-277.

93. Kharia AA, Hiremath SN, Singhai AK, Omray LK and Jain SK. (2010). Design and Optimization of Floating Drug Delivery System of Acyclovir, Indian J Pharm Sci.; 72(5): 599-606.

94. Sevgi T and Aybige G. (2010). Evaluation of Chitosan/ Alginate Beads Using Experimental Design: Formulation and in Vitro Characterization, AAPS Pharm Sci Tech, 11(1): 460-466.

95. Nagarwal RC, Srinatha A and Pandit JK. (2009). In situ forming formulation: development, evaluation, and optimization using 3^3 factorial design. AAPS Pharm Sci. Tech.; 10(3): 977-84.

96. Chudiwal PD, Pawar PL, Nagaras MA, Mandlik SK, Pandya SV and Wakte P. (2009). Statistical Evaluation and Optimization of Influence of Viscosity and Content of Polymer on Floating Microcapsules of Clarithromycin, Int. J Pharm Tech Res. 1(4): 1366-1372.

97. Ramesh CN, Srinatha A and Jayanta KP. (2009). In Situ Forming Formulation: Development, Evaluation, and Optimization Using 3^3 Factorial Design, AAPS Pharm Sci. Tech.; 10(3): 977-984.

98. Hosmani AH, Kasture PV, Gonjari ID and Karmarkar AB. (2009). Study of formulation variables on properties of glipizide mucoadhesive microcapsules by factorial design, DARU, 17(4): 236-244.

99. Sanap GS. (2009). Formulation and evaluation of mucoadhesive beads of glipizide using 23 factorial design, Journal of Pharmacy Research, 2(5): 934-938.

100. Yogesh ST, Vinayak SM and Shashikant CD. (2009). Use of carbomers to designmucoadhesive microcapsulesfor an anti- h. Pyloridrug, clarithromycin International Journal of Pharm Tech Research, IJPRIF, 1(4): 1421-1428.

101. Shahi SR, Shinde NV, Agrawal GR, Shaikh SA, Shaikh SS and Somani VG *et al.* (2008). Statistical optimization of gastric floating system for oral controlled delivery of Clarithromycin, Rasayan J. Chem, 1(2): 367-377.

102. Tabbakhian M, Sharifian A and Shatalebi MA. (2008). Preparation and in vitro characterization of tretinoin-containing microcapsules suited for dermatological preparations, Res in Pharm Sci.; 3(2): 31-40.

103. Varshosaz J, Tabbakhian M and Zahrooni M. (2007). Development and characterization of floating microballoons for oral delivery of cinnarizine by a factorial design, Journal of Microencapsulation, Micro and Nano Carriers, 24(3): 253-262.

104. Jayvadan KP, Rakesh PP, Avani FA and Madhabhai MP. (2005). Formulation and evaluation of mucoadhesive glipizide microcapsules, AAPS Pharm Sci. Tech, 6(1); E49-E55.

105. Martinez SC, Herrero VR and Negro S. (2004). Optimisation of Aciclovir poly (d,l-lactide-co-glycolide) microcapsules for intra vitreal administration using a factorial design study, Int. J of Pharmaceutics, 273: 45-56.

106. Li S, Lin S, Daggy BP, Mirchandani HL and Chien YW. (2003). Effect of HPMC and Carbopol on the release

and floating properties of Gastric Floating Drug Delivery System using factorial design. Int J Pharm. 253(1-2); 13-22.

107. Rajesh KM, Vikram UK. (2013). Application of novel concept of mixed solvency in the design and development of floating microcapsules of furosemide, Int. J Pharm Pharm Sci, 5(2): 167-175.

108. Anant P, Manish M, Amit KT, Bhaskar C and Kadam SS. (2003). Preparation and characterization of flurbiprofen beads by melt solidification technique, AAPS Pharm Sci. Tech, 4(4): 514-522.

109. Gohel MC and Amin AF. (1998). Formulation optimization of controlled release Diclofenac sodium microcapsules using factorial design, J of Controlled Release, 51(3): 115-122.

110. Nevin C and Nurhan ET. (1996). The preparation and evaluation of salbutamol sulphate containing poly (lactic acid-co-glycolic acid) microcapsules with factorial design-based studies, Int. J Pharmaceutics, 136(2): 89-100.