Overview on Recent Optimization Techniques in Gastro Retentive Microcapsules by Factorial Design

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Abstract- The aim of present literature collection on past work done on gastro retentive microcapsules by factorial design. Many researchers are getting attracted towards the design of experiments (DoE) in the optimization of drug delivery systems. Only a fraction of study was optimized till date. DoE software is easy to use, affordable and availability with the simple click of a computer mouse. The authors made sufficient afford to list out the various independent variables like different polymers used and the response generated from them viz., yield, size of microcapsules, drug trapefficacy and % cumulative drug release were used in the optimization of gastro retentive microcapsules.

Kay words: microspheres, factorial design, input, response

INTRODUCTION

Experimental designs can bedefined as the strategy for setting up experiments in such a mannerthat the information required is obtained as efficiently and precisely aspossible. Well-chosen experimental designs maximize the amount ofinformation that can be obtained for a given amount of experimentaleffort. Optimization techniques using the design of experiments(DoE), impregnated the field of pharmaceutical sciences around a few decades is gaining the attention of many researchers. The first bibliographic report onthe coherent use of optimization published in 1967, on optimization of Sodium salicylate tablets by factorial design (FD). Despite tremendousadvances in various techniques of drug administration, the oral route stands on top as it remains the most natural way of administration, low cost, easy to admin andimproved compliance of the patient. More than50% of the commercially available drug delivery systems are oral.The oral administration systems of prolonged-release drugs are quitepopular, that is, a series of ventures in the conventional dosage forms. In general, prolonged drug release systemsfor oral use solid dosage forms release drugs by the mechanism ofdiffusion. Most of the DoE bibliographic hearsays in this group focus on optimizationthe echelons of these polymers used for controlling the rate of release. DoE optimizationin the administration devices of the oral extended-release matrix began at the beginning of1980 [1].

The usualindependent variables in DoE in designing floating microcapsules were the amounts of polymers or other ingredients. Several types of polymers (natural, semi-synthetic, synthetic) and the type of gastro retentive dosage form (floating microcapsules) were enlisted in table 1. The use of experimental statistical designs in oral optimization of prolonged-release floating microcapsulestogether with the selected drugs [2].

Design of experiments and optimization techniques in pharmaceutical research

The DoE is a well-organizedprocess forplanning trials so that the data gained can be assessed toyield valid and objective assumptions. Optimization of a formulation or process is finding the bestpossible composition or operating conditions. Determining sucha composition or set of conditions is an enormous task, probablyimpossible and certainly unnecessary. So, in practice, optimizationmay be measured as the search for a result that is acceptable and atthe same time the best likely within a restricted field of search. Theintention of optimization is to regulate quantitatively the stimulus ofthe dissimilar factors composed on the response variables. The number oflevels is generally constrained to two, but adequate experiments are performed to allow for interaction among factors.

Experimental designs have long been engaged to optimize numerousindustrial goods and/or procedures, in that factorial designsaregaining the attraction.

DoE Steps

- Problem statement
- Set objectives
- Choose the variables (factors, levels, and ranges)
- Shortlist the variables
- Choose response variable(s)

- Choose experimental design
- Run the experiment
- Statistical analysis of the result
- Conclusions and recommendations

DOE presentations in process development

- Improve process yield
- Reduce variability
- Reduce development time
- Reduce overall costs

DOE aims

- Determine significant variables (factors).
- Regulate where to set important factors to optimize response.
- Govern where to set factors to diminish response variability.
- A consequenceof the uncontrollable factors.

DOE applications in design

- Evaluate and compare alternatives
- Evaluate material alternatives
- Product robustness
- Determine key design parameter

Optimizing Oral gastro retentive microcapsules

A comprehensive literature huntmade by the authors inpharmaceutical journals and texts discloses that the DoE optimizationprocedures have been betrothed for almost all dosage forms. This article highlights DoE optimization techniques (factorial designs) so far adopted in gastro retentive microcapsules.Earlier attempts so far did on gastro retentive microcapsules by factorial design were shown in table 1.

Table 1: Past work done on the factorial design on gastro retentive microcapsules

Drug candidate	Polymers used	Design	Reference
Carvedilol phosphate	Karayagum and Carboxymethyl locust bean gum	3^2 fullfactorial design	Bibek et al., 2019 [3]
Cefixime Trihydrate	Alginate- chitosan	3^2 fullfactorial design	Sindhumol, 2018 [4]
Metoclopramide Hydrochloride	Eudragit S100, Eudragit L100, Eudragit RS 100&RL 100 and Ethyl Cellulose (EC)	3^2 fullfactorial design	Monika et al., 2018 [5]
Clopidogrel bisulphate	HPMC K15 and Sodium bicarbonate	3^2 full factorial design	Sanjeevani et al., 2018 [6]
Metronidazole	Carbopol934P	3^2 fullfactorial design	Bolai, 2018 [7]
Saxagliptin	Sodium alginate and HPMC K4M.	3^2 fullfactorial design	Talat Farheen et al., 2018 [8]
quetiapine fumarate	EC,HPMC (K4M, K15M & K100M) and Chitosan	2^{5-2}factorial design	Someshwar et al., 2018 [9]
Sildenafil citrate	*Azadirachita indica* gum	3^2 fullfactorial design	Vijayavani and Vidyavathi, 2018 [10]
diclofenac sodium	Tamarindseed gum-hydrolyzed polymethacrylamide-g-gellan (h-Pmaa-g-GG) composite beads	3^2 fullfactorial design	Gouranga et al., 2018 [11]
Ibuprofen	Acetylatedplantain starches	3^2 fullfactorial design	Adenike and Tokoni, 2018 [12]
Lafutidine	HPMCK4M,calcium carbonate and sodium alginate	2^3full factorial design	Ritesh et al., 2018 [13]
dipyridamole	HPMC K4M, and EC	3^2 fullfactorial design	Vanshiv et al., 2017 [14]
Repaglinide	*Dioscorea dumetorum* and *Dioscorea oppositifolia*	3^2 fullfactorial design	Adenike et al., 2017 [15]

osartan potassium	EC	3^2 fullfactorial design	Gokul et al., 2017 [16]
Amoxicillin	EC, carbopol-934P	3^3 fullfactorial design	Hardenia and Gupta, 2016 [17]
Carbamazepine	Eudragit RL 100	2^2 fullfactorial design	Nusrat et al., 2016 [18]
Clarithromycin	Pullulan acetate	2^3 fullfactorial design	Mishra et al., 2016 [19]
Carvedilol	Carbopol940, HPMC, Sodium bicarbonate and Citric acid	3^2 fullfactorial design	Khalid, 2016 [20]
cefditoren pivoxel	HPMC K4M and EC	3^2 fullfactorial design	Swathi 2016 [21]
Amoxicillin	Carbopol-934P	3^3 fullfactorial design	Anu,2016 [22]
Diltiazem HCl	Sodiumalginate and HPMC K4M	3^2 fullfactorial design	Nareshand Shrikant, 2016 [23]
Ramipril	Sod. CMC, HPMC K4M Carbopol-934, Sodium bicarbonateand Citric acid	3^2 fullfactorial design	Iftequar, 2016 [24]
Sitagliptin	HPMC K4M and Psyllium husk	3^2 fullfactorial design	Sushil et al., 2016 [25]
Carvedilol	Sodiumalginate and sodium CMC	3^2 fullfactorial design	Sakhare et al., 2016 [26]
Paclitaxel	Acacia, Carbomer 941, hypromellose K-15, methyl cellulose, povidoneK-30, PEG 6000, gelatin, Sodium alginate, chitosan	2^4Factorial design	Chinmaya et al., 2016 [27]
Loratadine	EC, PVA	3^2 fullfactorial design	Sonam and Kamla, 2016 [28]
Melatonin	Chitosan/Pluronic® F127	3^2 fullfactorial design	Marieta et al., 2016 [29]
Salbutamolsulphate	Poly(lactic acid-co-glycolic and PVA	2^3 fullfactorial design	Nevin et al., 1996 [30]
Ibuprofen	Poly(ε-caprolactone)–poly(ethylene glycol)–poly(ε-caprolactone) copolymer	2^4 fullfactorial design	Azouz et al., 2016 [31]
Ketoprofen	EC and EudragitRL 100	3^3 fullfactorial design	Sanjoy et al., 2016 [32]
Diltiazem HCl	Polycarbonate	2^3 full factorial design	Mangal et al., 2015 [33]
Carvedilol	HPMCK100M and Sodium bicarbonate	3^2 fullfactorial design	Raghavendra et al., 2015 [34]
Ranitidine HCl	HPMC K100M and Carbopol 971	3^2 fullfactorial design	Jabbar, 2015 [35]
Captopril	Xanthan gum and HPMC K100M, calcium carbonate	3^2 fullfactorial design	Ahsan, 2015 [36]
Prazosin HCl	HPMC K100	2^3factorial design	Vanitha, 2015 [37]
Zolpidem Tartarate	EC and HPMC 5 cps	2^3 fullfactorial design	Sachin, 2015 [38]
Carvedilol	EC and HPMC	3^2 fullfactorial design	Nila et al., 2014 [39]
Acyclovir	EC and Carbopol 940	3^2 fullfactorial design	Kyada et al., 2014 [40]

Cefpodoxime Proxetil	Eudragit S100	3^2 fullfactorial design	Monica, 2014 [41]
Ramipril	Eudragit E100. Glycerol monostearate and sodium lauryl sulfate	3^2 fullfactorial design	Tushar et al., 2014 [42]
Glipizide	HPMCK4Mand Carbopol934	3^2 fullfactorial design	Sujata et al., 2014 [43]
Cefdinir	Gum Karaya	2^3 fullfactorial design	Sarath and Suresh, 2014 [44]
Ziprasidone HCl	EC and PVP	2^3 fullfactorial design	Praneeth et al, 2014 [45]
Pioglitazone	HPMC K100 and Carbopol 934	3^3 fullfactorial design	Wattamwar et al., 2014 [46]
Clopidogrel bisulphate	Xanthangum, HPMC K15M, HPMC K4M and Sodium bicarbonate	2^3full factorial design	Bhadouriya et al. 2013 [47]
Verapamil HCl	HPMC K4M, Sodium bicarbonateand Citric acid	3^2 fullfactorial design	Shahi et al. 2013 [48]
Duloxetine HCl	Eudragit L-100	3^2 fullfactorial design	Anupama, 2013 [49]
Atenolol	Poly Vinyl Alcohol	3^2 full factorial design	Bhadouriya et al. 2013 [50]
Cefpodoximeproxetil	Chitosan	3^2 fullfactorial design	Nappinnai and Sivaneswari, 2013 [51]
Agrochemical 2,4-D	EC, HPMC, cellulose acetate butyrate butyryle	2^2 factorial design	Fatima et al., 2013 [52]
Captopril	HPMC K4M and EC and Sodium alginate	3^2 fullfactorial design	Durgavale et al. 2012 [53]
Captopril	Eudragit RL-100 and EC	3^2 fullfactorial design	Sanket Gandhi, 2012 [54]
Ranitidine HCl	Eudragit RL-100.	2^3full factorial design.	Jhansipriya, 2012 [55]
Captopril	HPMC K4M	3^2 fullfactorial design	Devesh, 2012 [56]
Ciprofloxacin HCl	EC and HPMC 5 cps	2^3 fullfactorial design	Narendra et al., 2012 [57]
Tolperisone	EC and HPMC 15 cps	2^3 fullfactorial design	Pooja et al., 2012 [58]
Celecoxib	Eudragit L-100 and PVP	3^2 fullfactorial design	Shahzad et al., 2012 [59]
Cephalexin	EC and PVA	3^2 fullfactorial design	Kamini and Rajesh, 2011 [60]
Acyclovir	EC	3^2 fullfactorial design	Vinod, 2011 [61]
Acyclovir	Poly (D, L Lactide-co-glycolide)	2^3 fullfactorial design	Bhosale, 2011 [62]
Metformin HCl	EC, HPMC and Sodium Alginate, sodium bicorbonate	3^2 fullfactorial design	Masaet al., 2011 [63]
Risedronatesodium	PLGA	2^4 fullfactorial design	Maha et al., 2011 [64]
Stavudine	EC	3^2 fullfactorial design	Sanjay Dey et al., 2011 [65]
Pioglitazone HCl	EC and HPMC K100M	3^2 fullfactorial design	Satish, 2010 [66]
Acyclovir	psyllium husk and HPMC K4M	3^2 full factorial design	Kharia et al., 2010 [67]
Bovine serum albumin	Chitosan and Alginate	3^2 fullfactorial design	Sevgi and Aybige, 2010 [68]

Metformin	Sodium alginate and Gellan gum	3^3 full factorial design	Nagarwal et al., 2009 [69]
Clarithromycin	HPMC 15M, HPMC K4M, HPMC 100LV and EC.	3^2 fullfactorial design	Chudiwal et al., 2009 [70]
Metformin	sodium alginate and gellan gum	3^3 fullfactorial design	Ramesh, 2009 [71]
Glipizide	Polycarbophil and Sodium Alginate	3^2 fullfactorial design	Hosmani et al, 2009 [72]
Glipizide	sodium alginate, carbapol 974P and SCMC	2^3 fullfactorial design	Sanap, 2009 [73]
Clarithromycin	carbopol 934 P & polycarbophil	3^2 fullfactorial design	Yogesh et al., 2009 [74]
Clarithromycin	HPMC K4M	3^2 fullfactorial design	Shahi, 2008 [75]
Tretinoin	cellulose acetate, Polyvinyl alcohol	2^3full factorial design	Tabbakhian et al., 2008 [76]
Cinnarizine	Eudragit S100, Eudragit RL,	3^2 fullfactorial design	Varshosaz et al., 2007 [77]
Glipizide	Chitosan	3^2 fullfactorial design	Jayvadan et al., 2005 [78]
Acyclovir	Poly(d,l-lactide-co-glycolide)	2^2 fullfactorial design	Martinez et al., 2004 [79]
Propranolol	HPMC K4M, K100LV and Carbopol P934	2^3 full factorial design	Li, et al., 2003 [80]
5-fluorouracil	Poly(D,L-Lactide-Co-Glycolide)	3^2 fullfactorial design	Rajesh et al., 2003 [81]
Flurbiprofen	Cetyl alcohol	3^2 fullfactorial design	Anant et al., 2003 [82]
Diclofenac sodium	sodium alginate	3^3 fullfactorial design	Gohel and Amin, 1998 [83]

Note: The percent yield, Particle size, entrapment efficiency, the initial burst release (%) and%Cumulative drug release were designated as dependent variables the above cases

Current and Future Developments

With the arrival of newer, urbane technologies, the task ofdrug delivery has become more complicated, involving a greater numberof resources in terms of cost, time, and energy. To dodge thesedevelopmental hiccups, implementation of DoE analytical tools is used. Particularly, when judgment the precise compromise is notstraight forward, an industrialist should mandatorilyreflect the use of optimization studies.DoE techniques have been applied with fruition on almost all kindsof drug delivery systems, not only for optimizing the formulations buttheir processes too. Nevertheless, there are many new drug deliveryapplications awaiting demonstrations. The pivotal benefits of DoEhave not been thoroughly investigated in some newer drug deliveryareas such as gene delivery, peptide delivery, reverse micellar systems,dendrimer based delivery systems and the like. Understandingthe formulation/method variables sensibly using experimentaldesigns will help in attaining the anticipated goals with remarkable ease.

CONCLUSIONS

The literature search unquestionably ratifies the progressively increasingpopularity of DoE in designing formulation. Verily, the numberof optimization approaches would be much more in the drug industry,where DoE methods are applied much more frequently. Because only aminute fraction of industrial studies are reported, most investigationsremain as only in-house information. Nevertheless, the DoE usage isfar from being adopted as a standard practice. With the easyavailability and affordability of DoE software, these powerful tools canbe implemented with the simple click of a mouse. Some key constraints that depend upon the experimenter but not upon thesoftware. These include choosing suitable input variables (factors), output variables (responses)and setting appropriate factor ranges/levels,managing the experimentation, interpreting numeric outcomes andgraphic manifestations of the findings, presenting the results, and finallydeciding whether to continue further with process optimization or justrun confirmatory experiment(s) to validate DoE. Hope the effort made by the authors may help in finding new research ideas.

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