Research article Available online www.ijsrr.org ISSN: 2279–0543

International Journal of Scientific Research and Reviews

Formulation of Novel Co-Processed Excipient by Microwave Drying Method and Evaluation of Sustained Release Tablet Prepared by Direct Compression

Vipul P. Patel[1] and Zil P. Patel[2]*

[1]MEFGI-Faculty of Pharmacy, Marwadi University, Rajkot, Gujarat
[2]Kalol Institute of Pharmacy; KIRC Campus, Gandhinagar
Email: [1] v_pharmacy@yahoo.co.in. [2]zil_patel177@yahoo.co.in

ABSTRACT

A directly compressible co-processed excipient composed of a hydrophilic natural gum and ethyl cellulose was developed by microwave drying method. Sustained release co-processed excipient was formulated and Propranolol HCl was used as model drug. The tablets were prepared by direct compression method. Xanthan gum and methylcellulose were used as release retardant polymers. Their ratio was optimized using simple 2^2 full factorial design. The pre-compression and post-compression parameters were evaluated for the final tablet dosage form. Drug release at 1 hr and 12 hrs were studied as independent factors. Ethyl cellulose exhibited a negative impact on drug release from at 12hrs. The optimized formulation was evaluated and stability study

KEYWORDS: Co-processed excipients, Sustained release, microwave drying, direct compression,

***Corresponding author**

Zil P. Patel

Kalol Institute of Pharmacy;

KIRC Campus, Gandhinagar

Email: zil_patel177@yahoo.co.in

INTRODUCTION

The conventional oral dosage forms, such as tablets and capsules are formulated to release the active drug at once after administration to obtain rapid, repeated dosing of the drug which may lead to the peril of dose variation and complete systemic drug absorption. This lead to need of a formulation with control release that maintains a near constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. The purpose of any drug delivery system is to make available a therapeutic amount of drug to the proper site in desired proportion.[1, 2] The International Pharmaceutical Excipient Council (IPEC) definition of a co-processed excipient is "a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change". Co-processed excipients provide improved excipients characteristics like flow property and compression characteristics. Directly compressible co-processed excipients available in market are Pharmatose, Tablettose, Avicel grades, etc.[3]

Microwave drying technique has shown growing application in pharmaceutical industry. It is a rapid drying method with high efficiency compared to other conventional methods[4]. It's safe use for drying of pharmaceutical grade powders was studied and may be its application can be extended further[5].

MATERIALS AND EQUIPMENT

The model drug propranolol was obtained as gift sample from hetero labs, Hyderabad. The polymer ethyl cellulose (Ethocel) was obtained as gift sample from Colorcon, Mumbai. Xanthan gum and starch were purchased from Chemdyes Corporation, Ahmedabad. Microwave model (IFB 25SC4) was used for drying the granules.

Preparation of Propranolol HCl tablets containing co-processed excipient

A 2^2 full factorial design with one centre point was used to optimize the ratio of Ethyl cellulose and Xanthan gum. Sieve all excipients through 60# sieve. Mix for 15 minutes and granulate using suitable binder (starch paste 10%). Pass through sieve no.20 and spread in a borosilicate petridish of large size (R10cm). Dry granules in a microwave for 4 minutes at maximum power. Retain the prepared co processed excipients on sieve no 40. The process variables like microwave power, feed load and drying time were derived by preliminary trial methods. The prepared co-processed excipients were mixed with active drug components and the other formulation ingredients in a V shaped mixer for 15 min and compressed in rotary tablet punching machine.

Table 1: Levels of Independent variables and dependent variables

Independent variable	Lower level	Upper level	Mean	Dependent variables
A: Ethyl cellulose	-1 (70)	+1 (150)	0 (110)	Response 1 % CDR 1 hr
B: Xanthan Gum	-1 (50)	+1 (130)	0 (90)	Response 2 %CDR 12hr
No. of replicates	03			

The composition of all the five batches as per the factorial design are illustrated in table no.2

Table 2: Formulation of batches for optimization design

Formulation ingredients	F1	F2	F3	F4	F5
Formulation of co processed excipient					
Ethyl cellulose	70	110	150	150	70
Xanthin gum	130	90	130	50	50
Formulation of Propranolol HCl Tablet containing co processed excipient					
Propranolol HCl	80	80	80	80	80
Co-processed exp	200	200	200	200	200
MCC	20	20	20	20	20
Starch paste	q.s.	q.s.	q.s.	q.s.	q.s.
Mg stearate	1%	1%	1%	1%	1%
Talc	1%	1%	1%	1%	1%
Total	300	300	300	300	300

Evaluation of co-processed excipients

1. % Fines

The prepared co-processed excipients were pre weighed and passed through a 60# sieve. The fines are collected and weighed separately.

%Fines = wt of fines/ total wt *100

2. Bulk density and Tapped density

25gm of sample was filled in a 100ml measuring cylinder and tapped 50 times. The initial and final volumes were measured. The densities were calculated as below formula.

Bulk density = W/ V_0

Where, W is the weight of polymer and V_0 is the bulk volume of the polymer.

Tapped density = W /V_f

where, W is the weight of powder, V_f is the tapped volume of the powder.

3. Hausner's Ratio (HR) and Carr's Index (CI)

The pre-calculated tapped densities and bulk densities are used in the following equations to determine HR and CI to evaluate the compressibility characteristics and flow property.

Hausner's ratio (HR) = Tapped density/ Bulk density

Carr's index (CI) = (Tapped density - Bulk density) / Tapped density

The standard table for reference are given in Table no.2 of chapter 1(Introduction)

4. Angle of Repose

Fix a glass funnel at 2.5cm height(fix) using a burette stand and place a graph paper below. 25gm of sample is allowed to flow through the funnel. The circumference of the pile formed is marked with a pencil and the average diameter is measured.

$$\Theta = \tan^{-1} (h/r)$$

Where 'h' is height of pile and 'r' is radius of pile

The standard table for reference are given in Table no.2 of chapter 1 (Introduction).

5. Granular friability (F)

10gm of sample was placed in a Roche friabilator and rotated for 4min at 25rpm. The sample sieved through 60# screen and measure the co processed excipients retained on the sieve.

F= initial wt – final wt/initial wt*100

< 1% Indicates resistance to loss of weight due to facture and abrasion during transportation[6].

6. Dilution potential

The prepared co-processed excipients were mixed with Paracetamol (poorly compressible drug) in an increasing percentage in order of 10% until the mixture can be compressed to form tablets of acceptable hardness. The dilution potential is the maximum %weight of drug that can be incorporated into co processed excipients. A value of greater than 30% is desirable.

Evaluation of Propranolol HCl tablets

In vitro drug release profile- %CDR 1hr and %CDR 12 hr

As per USP monograph for Propranolol HCl ER capsule[7, 8] the dissolution of tablets was carried in two different media in USP dissolution apparatus I at 100rpm and 37±2°C. Aliquots of one ml sample were withdrawn at pre determined time interval (replaced with 1ml dissolution media) and the amount of dug was drug was determined by measuring the UV absorbance at 288nm in a UV spectrophotometer. The sample tablets are first place in 900ml of 0.1 N HCl for two hours and then immediately placed in 900ml 6.8pH phosphate buffer for remaining time.

Fitting of Mathematical Models

Drug release profiles data of the optimized formulation was fitted to various mathematical models (Zero-order, First-order, Higuchi, Hixon Crowell and Krosmeyer Peppas) in order to describe the kinetics of drug release, best goodness-of-fit test ($R2$) were taken as criteria for selecting the most appropriate model as per table given below:

The prepared batches were subjected to stability study for two months at ambient conditions

RESULT AND DISCUSSION

Evaluation of co-processed excipients

The results for evaluation parameters for experimental batches are discussed hereby. The results for evaluation of co-processed excipients are given in table 5.12. while the tables 5.13 and 5.14 exhibit the tablet characteristics; pre- compression and post-compression parameters respectively.

Table 3: Evaluation of experimental batches for Microwave drying method (compression characteristics of co-processed excipients)

Batches	% Fines	Bulk density(mg/ml)	Tapped density(mg/ml)	Angle of repose (°)	Carr's Index	Hausner's Ratio	Dilution Potential (%)
F1	15.6	0.388±0.01	0.42±1.02	26.113±0.04	7.407±0.05	1.08±0.05	40
F2	16	0.363±1.12	0.4±0.65	24.443±0.04	9.090±0.01	1.1±0.07	50
F3	14	0.438±0.58	0.488±0.33	23.682±0.05	10.204±0.21	1.113±0.42	60
F4	16.8	0.373±0.78	0.404±0.06	25.676±0.14	7.547±0.03	1.081±0.08	50
F5	18.8	0.381±0.23	0.429±1.12	24.057±0.19	11.111±0.01	1.125±0.02	50

*the values represent mean with standard deviation, n=3

The results obtained from the evaluation of co-processed excipients experimental batches depict excellent flow properties and good compression characteristics. The dilution potential is near to 50 % which is desirable.

Evaluation of Propranolol HCl tablets

The experimental batches were evaluated for thickness, hardness, friability, uniformity of weight and drug content. The results obtained are specified in table no.4.the effect of ethyl cellulose and xanthin gum ratio on the drug release at 1 hr and 12hrs are graphically represented in fig no.1 and 2 respectively

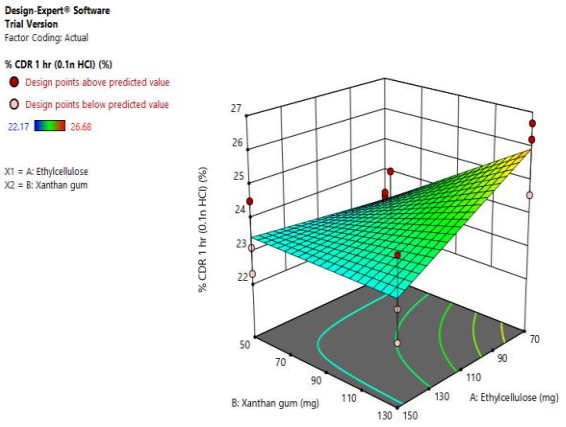

Figure 1: Effect of Factor A and B on %CDR 1hr (0.1N HCl): 3D Surface Plot

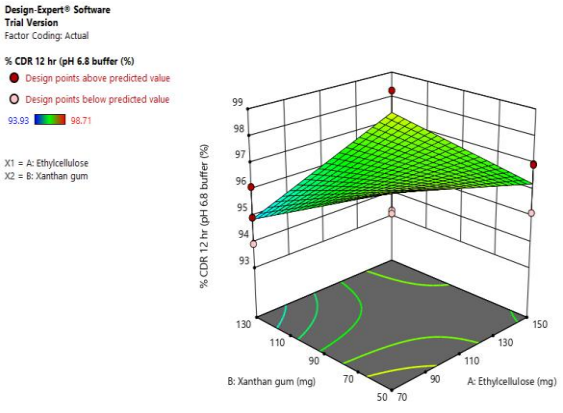

Figure2: Effect of factor A and B on %CDR 12hr (6.8 pH phosphate buffer)

The concentration of ethyl cellulose has a negative effect on % CDR 1hr (0.1N)HCl. As the concentration of ethyl cellulose increases the drug release decreases. While as the concentration of xanthin gum increases the drug release also increases. Xanthin gum is a hydrophilic polymer and swells to form a matrix. It is responsible for the burst release of the medicament. The interaction AB is significant in the given model which indicates that both the factors together have influence on the given response. The concentration of ethyl cellulose has a positive effect on % CDR 12hr in 6.8pH phosphate buffer. As the concentration of ethyl cellulose increases the drug release increases. While as the concentration of xanthin gum increases the drug release also decreases. Xanthin gum is a hydrophilic polymer and swells to form a matrix. It helps to keep the tablet intact and slows down drug release. The interaction AB is signify-cant in the given model which indicates that both the factors together have influence on the given response

Table 4: Evaluation of experimental batches for Microwave drying method

Batch no.	Thickness* (mm)	Uniformity of Weight (mg)	Hardness* (kg)	Friability (%)	Drug content (mg)
F1	3.41±1.35	301±3.28	5.4±1.5	0.05	80±1.02
F2	4.12±1.45	298±2.21	5.7±1.8	0.41	79±0.04
F3	3.23±1.61	300±2.72	5.8±1.5	0.30	81±0.05
F4	4.16±1.23	299±1.28	5.5±1.5	0.51	78±1.24
F5	3.52±1.45	295±4.21	5.5±1.8	0.23	82±0.05

*the values represent mean with standard deviation, n=3

The results for uniformity of weight, friability and drug content fall within the pharmacopoeia limits as per IP 2010 indicating that the tablet samples pass the respective test. Thickness and Hardness are within acceptable range.

Drug release kinetics

A 12 hr dissolution study was performed for experimental batches F1-F5 and the %CDR vs. Time graph was plotted as shown in fig.3

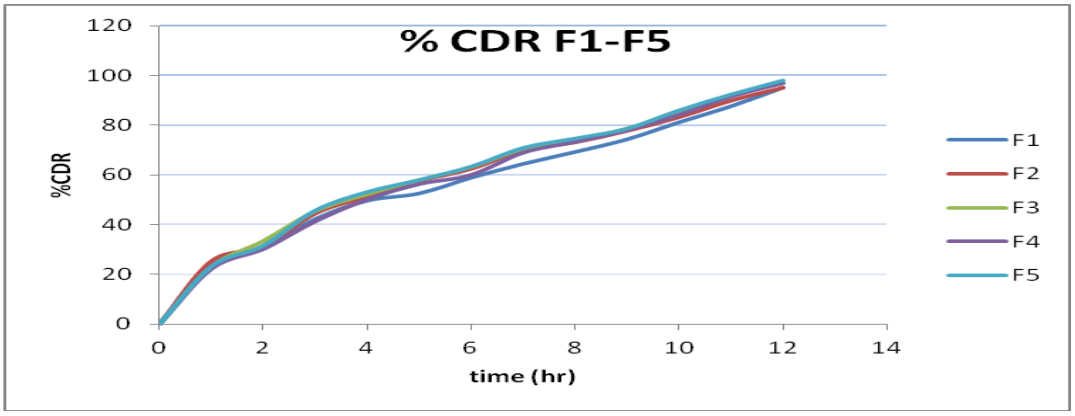

Figure 3: Dissolution profile for experimental batches F1-F5

Fitting of mathematical model

The drug release profile was studied and different mathematical models were studied to observe the best fitted model. The R^2 (Regression) value was calculated and n value was determined for determination of release kinetics.

Table 5.15: Fitting of mathematical model experimental batches F1-F5

Model	F1	F2	F3	F4	F5
Zero order kinetics	0.9534	0.9461	0.9874	0.9652	0.9456
First order kinetics	0.8842	0.9178	0.8789	0.8745	0.8563
Higuchi model	0.9861	0.9945	0.9958	0.9891	0.9905
Krosmeyer's peppas model	0.9862	0.9901	0.9973	0.9889	0.9934
N (diffusion exponent)	0.5485	0.5472	0.5694	0.5548	0.5984

The R^2 value was compared and the highest value was obtained for Higuchi model. The experimental batches were seen to follow the Higuchi model for diffusion through polymer matrix. The n value for all batches is in near to 0.5, thus the release mechanism observed from the n value is Fickian diffusion.

Stability study

The experimental batches were subjected to stability study for two months at ambient conditions (25°C, 65% RH).The results for drug release and drug content were compared with the initial data with student's t test. During the Stability study no remarkable changes were observed in drug content. No significant changes were observed in %CDR of the Propranolol HCl SR(Sustained Release) tablets.

CONCLUSION

The microwave drying method proves to be an efficient drying technique with further adaptability in pharmaceutical industries. The co processed excipients composed of ethyl cellulose and xanthin gum exhibit excellent flow properties and better compression characteristics. Presence of ethyl cellulose depicts Higuchi model of release kinetics and provides a fickian diffusion (n = 0.5) It can be concluded that the prepared novel co processed formulations can be suitably used for designing sustained release formulation of different BCS class I drugs. The tablets can be directly compressed with incorporation of minimum 50 % W/W of drug alone (or drug along with other excipients) and an extended drug release for 12 hours may be obtained.

REFERENCES:

1. YW. C. *Novel Drug Delivery System. Revised and Expanded.*. New York: CRC Press; 2005; 2
2. Vamsy KA, Srinath KR CP. Formulation development and evaluation of divalproex sodium extended release tablet. *Int J Res Pharm Biomed Sci*. 2011; 2: 809-832.
3. Gohel MC, Jogani PD. A review of co-processed directly compressible excipients. *J Pharm Pharm Sci*. 2005; 8(1): 76-93.
4. Wang W, Zhao C, Sun J, et al. Quantitative measurement of energy utilization efficiency and study of influence factors in typical microwave heating process. *Energy*. 2015; 87: 678-685. doi:10.1016/j.energy.2015.05.036.
5. Mcloughlin CM, McMinn WAM, Magee TRA, Member A. Microwave Drying of Pharmaceutical Powders. *Food Bioprod Process*. 2000; 78(2): 90-96. doi:10.1205/096030800532798.
6. Certificate A. Indian Pharmacopoeia The Pharmacopoeia Commission ; Govt. ofIndia, Ministry of Health & Family Welfare . Sector 23, Raj Nagar, Ghaziabad; 2010; 1: 412.
7. USP Monographs_ Propranolol Hydrochloride Extended-Release Capsules. *pharmacopoeial forum USP29–NF24*. 2006; 1843. http://www.pharmacopeia.cn/v29240/usp29nf24s0_m70874.html. Accessed June 10, 2018.
8. Propranolol Hydrochloride Extended- Release Capsules. *US FDA*. 2010;(c):1-2.