CHAPTER III
OPTIMIZATION OF PHARMACEUTICAL PRODUCT FORMULATION BY FACTORIAL DESIGNS

The word "Optimize" means to make as perfect, effective or functional as possible. Optimization of product or process is determination of experimental conditions resulting in its optimal performance. Optimization has been defined as the implementation of systemic approaches to achieve the best combination of product and/or process characteristics under a given set of conditions. With respect to the drug formulations or pharmaceutical process, optimization is a phenomenon of finding "the best" possible composition or operating conditions. Although several optimization procedures are available to the pharmaceutical scientist, in general the procedure consists of preparing a series of formulations, varying the concentrations of formulation ingredients in some systemic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to be optimal.

Optimization of pharmaceutical formulations involves choosing and combining ingredients that will result in formulation whose attributes conform to certain prerequisites. The choice of the nature and quantities of additives (or excipients) to be used in a formulation has to be based on some rational. The optimization techniques will help in fixing the quantities or levels of the excipients.

Optimization techniques are relatively new to the practice of pharmacy. In general the
traditional procedure consists of preparing a series of formulations, varying the concentrations of the formulation ingredients in some systematic manner. These formulations were then evaluated according to one or more attributes such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests a particular formulation or series of formulations may be predicted to be optimal. The predicted optimal formulation has to be prepared and evaluated to confirm its quality.

The formulation is generally optimized according to a single attribute. Optimization by Factorial Design:

The modern approach for optimization is through the use of statistical techniques. Optimization using factorial designs is an efficient technique used in formulation optimization. The optimization procedure is facilitated by construction of a mathematical equation that describes the experimental results as a function of the factor levels. A polynomial equation can be constructed in the case of a factorial design where the coefficients in the equation are related to effects and interactions of the factors. The equation constructed from a $2^n$ factorial experiment is as follows:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \ldots + \beta_{12} x_1 x_2 + \ldots + \beta_{123} x_1 x_2 x_3$$

Where $y$ is the measured response, $x_i$ is the level of the $i$th factor, $\beta_1, \beta_2, \beta_3 \ldots$ represent coefficients computed from the responses of the formulations in the design and $\beta_0$ represents intercept.
Full Factorial Design (FFD): Factorial experiments with two-level factors are used widely because they are easy to design, efficient to run, straightforward to analyze, and full of information. A full factorial design contains all possible combinations of a set of factors. This is the most foolproof design approach, but it is also the most costly in experimental resources. The full factorial designer supports both continuous factors and categorical factors with up to nine levels. Factorial designs with only two-level factors have a sample size that is a power of two (specifically $2^f$ where $f$ is the number of factors). When there are three factors, we have eight formulations, a total of eight responses.

Recent Research on Optimization by Factorial Designs

Literature on optimization by factorial designs is rather scanty. A summary of recent research on optimization by factorial designs is given in Table 3.1.
<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Drug</th>
<th>Therapeutic Category</th>
<th>Purpose/Objective</th>
<th>Factors/Variables</th>
<th>Result</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Itraconazole</td>
<td>Anti fungal</td>
<td>A 2&lt;sup&gt;3&lt;/sup&gt; factorial study on Optimization of formulation ingredients for PLGA nanoparticles containing Itraconazole (500µg/ml) could be achieved.</td>
<td>PLGA, Benzyl benzoate, Itraconazole</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Famotidine</td>
<td>Anti ulcer</td>
<td>A 2&lt;sup&gt;3&lt;/sup&gt; factorial study on Development of optimized floating drug delivery system of famotidine</td>
<td>Methocel K15M, Methocel K100, Sodium bicarbonate</td>
<td>Optimized formulation exhibited a Floating lagtime 37sec, floating time 10h, In-vitro release 87% up to 10h.</td>
<td>5</td>
</tr>
</tbody>
</table>
Ibuprofen (NSAID)

A 2\textsuperscript{3} factorial study on Optimization of buoyant beads containing ibuprofen. Sodium alginate, Magnesium stearate, Liquid paraffin. Optimized formulation with entrapment efficiency of 84.07\% gave drug release up to 8h.

Nifedipine (Calcium channel blocker)

A 2\textsuperscript{3} factorial study on formulation and optimization of nifedipine microspheres. Eudragit RL100 (1-2g), Stabilizer (0.1-0.5g), Drug/polymer ratio (0.05:1-0.1:1). Sustained drug release up to 12h was achieved with optimized formulation.

Topotecan (Anti-cancer)

A 2\textsuperscript{3} factorial study on Development of liposomal system for potent drug topotecan. Cholesterol (\%), phosphatidyl glycerols (\%), polyethylene glycols (\%), drug to lipid molar ratio. Drug entrapment 11.44\% and Prolonged drug release was achieved with optimized formulation.
<table>
<thead>
<tr>
<th>Polymer conc</th>
<th>Calcium chloride concentration</th>
<th>Crosslinking time</th>
<th>Particle size (µm)</th>
<th>Mucoadhesion %</th>
<th>Drug permeation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>39.9</td>
<td>79.98</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

97 % of mucoadhesion and 94.8 % drug permeation was achieved with optimized formulation.

**Simvastatin** (Anti hyperlipidemic)

A 2^3 factorial study on Optimization and Formulation of capsules loaded with simvastatin SLN.

Glyceryl monostearate: Stabilizer

Max maximum entrapment efficiency and sustained drug release was achieved with optimized formulation.

**Zolmitriptan** (Anti-depressant)

A 2^3 factorial study on Development of optimized formulation of Stearic acid, lecithin, Homogenization time

Entrapment efficiency of 81.36 % and drug release up to 24 h was achieved.
Optimization and Formulation of nasal gel of ondansetron for improving its bioavailability.

- Permeation enhancers (PEG400 1%/PPG 1%)
- Polymers (HPMC E15 1%)

Increased nasal residence time, increase in permeation rate was achieved with optimized formulation.

Development and optimization of fast dissolving tablet (FDT) with rapid disintegration and adequate hardness.

- Mannitol
- Camphor

Rapid Disintegration of 31sec, excellent hardness (4kg/cm²) was achieved.

Factorial study on PMMA Eudragit E 100 Optimized formulation.
Hypertensive development and optimization of transdermal drug delivery system. DMSO gave a release profile nearer to theoretical prediction.

Hydralazine HCl (Smooth muscle relaxant)

A 2\times 3 factorial study on development and optimization of mucoadhesive buccal tablets. Xanthum gum Carbopol HPMC increased bioavailability decreased side effects and increased patient compliance.

Simvastatin (Anti hyperlipidemic)

A 2\times 3 factorial study on formulation, optimization and characterization of Simvastatin nanosuspension. PVPK 30,SLS,organic to aqueous solvent ratio enhanced dissolution rate, fast onset of action.
Telmisartan (Anti-hypertensive) study on Evaluation of effect of SSG and βCD on the dissolution profile of telmisartan tablets. Sodium starch glycolate, βCD Optimized formulation containing SSG (55.714mg) and βCD (30mg) gave 70% of drug release in 30 min.

Captopril (ACE inhibitor) A 3² factorial study on Formulation of floating microspheres with increased residence time and controlled release. Ethyl Cellulose Eudragit RL-100 Increased residence time and drug release up to 24h was achieved.

Meloxicam (NSAID) A 2² factorial study on Development of orodispersible formulation Mannitol, Crosspovidone Rapid disintegration in 32 sec, fast release rate 99.5% within 30 min was achieved.
Theophylline (bronchodilator) 
A 3\(\times\)2 factorial study on Development of an optimized sustained release formulation. 
Guargum Hydroxypropylcellulose Sustained release rate over 12h was achieved. Release followed Korsmeyer Peppas model.

Propanolol hydrochloride (anti hypertensive drug) 
A 3\(\times\)2 factorial study on the effect of the polymer blends and the polymer concentration on drug release of propanolol hydrochloride matrix tablet HPMC K15M Carbopol 934P and Polymer concentrations Release rate decreased proportionally with increased concentration of Carbopol 934P and total polymer concentration.

Isoxsuprine hydrochloride 
A 3\(\times\)2 factorial study on HPMC K15M PVP K25 Drug was released for a
Preparation of an optimized sustained release tablet of isoxsuprine hydrochloride prolonged time up to 12h.

Losartan potassium (Antihypertensive)

A 2³ factorial study on Development of gastroretentive sustained release floating matrix tablet.

HPMCK15M Sodium bicarbonate Prolonged gastric residence time, Drug release up to 24h was achieved.

Ibuprofen (NSAID)

A 3² factorial study to Design of a sustained release micropellet dosage form of ibuprofen. HPMC K100M 16.7%, 33.3% & 50%. Drug release was 93.3% up to 24h.

Nateglinide (Anti diabetic drug)

A 3² factorial study on Development Sodium bicarbonate Ethyl cellulose Drug release was 98.33% up to 24h.
of a floating tablet of 
$\text{Na^+}$ teglinide to 
enhance its bioavailability 
and sustained action 
achieved.

23 Acyclovir (Anti-Viral) 
A 3\textsuperscript{2} factorial 
study on development 
of controlled release floating 
matrix tablets of Acyclovir. 
HPMC K15M, polyethylene 
one (Polyox WSR 303) 
Excellent floating behavior with floating 
duration greater than 12 h.

24 Diltiazem Hcl (Anti-Hypertensive) 
A 3\textsuperscript{2} factorial 
study on development 
of bilayer floating matrix 
tablets of Diltiazem Hcl to prolong 
a gastric residence time. 
HPMC K100M and Ethyl cellulose 
Drug release in the range of 95-100\% 
upto 12 hrs was achieved.
REFERENCES


