REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org

Formulation and Optimization of Immediate Release Tablets using Wet Granulation Method and Box-Behnken Design

Anjali Gupta[1], Vandana Mahawar[1], Shaily Chaudhary[1]*, Harish Kumar Tiwari[1], Vikas Patidar[1], Vishesh Bhaty[1], YashBairagi[1], Yashwant Choudhary[1], Aayushi Kushwaha[1], Akash Yadav[2]

[1*]Compfeeders Aisect College of Professional Studies, Pharmacy College, Rangwasa, Indore (M.P.), India
[2]IPS Academy College of Pharmacy, Knowledge Village, A.B. Road, Rajendra Nagar, Indore (M.P.), India

***Corresponding Author:** Dr. Shaily Chaudhary
*Head & Professor, Compfeeders Aisect College of Professional Studies, Pharmacy College, Rangwasa, Indore (M.P.), India, Email Id: s.shailychaudhary@gmail.com

Abstract
One of the most well-known over-the-counter medications is Paracetamol. Paracetamol is a Para-aminophenol derivative (N-acetyl-para-aminophenol) and has analgesic and antipyretic properties. The Paracetamol has high targeted action in the brain, it blocks an enzyme involved in Transmission of pain. Orphenadrine Citrate is one of the anticholinergic drugs that are used to treat painful muscle spasms, other similar conditions. It belongs to the ethanolamine category and antihistamine. Paracetamol is a BCS Class II drug having low solubility and high permeability and hence the basic objective was to produce immediate release tablets. Drug excipient interaction was investigated by placing vials containing drug excipient mixture at 45ºC±2ºC /75%±5% RH in wet and dry conditions which does not show any incompatibilities. The task of developing immediate release tablet is accomplished by varying the concentration of PVPK-30 and Sodium Starch Glycollate. Faster disintegration of the tablet administrated orally minimizes absorption time and improves its bioavailability in shorter period of time. The formulation development work was initiated with wet granulation method and a total of 4 formulations (A, B, C, D) were prepared.
The formulated tablets were evaluated for various pre-compression and post-compression parameters. Tablets were found to be satisfactory when evaluated for thickness, weight uniformity, in-vitro drug release, assay, disintegration time. The in-vitro drug release for optimized formulation A was found to be 99.34% for Paracetamol and 98.81% for Orphenadrine Citrate at the end of 35 minutes and showed satisfactory (assay) drug content (98.75% Paracetamol & 97.86% Orphenadrine). The in-vitro drug release of optimized batch compared with marketed formulation and dissolution profile was found to be similar. From this study, it was concluded that optimized A batch containing PVPK-30 (8%) and Sodium Starch Glycollate (5%) showed better characteristics of immediate release tablets.

Keywords: Immediate release, PVPK-30, Sodium Starch Glycollate, Paracetamol, Orphenadrine Citrate.

Introduction

The development of pharmaceutical formulations is a crucial process in drug delivery, ensuring that medications provide optimal therapeutic effects, safety, and patient convenience.[1] Among various dosage forms, immediate-release (IR) tablets are designed to disintegrate and dissolve rapidly in the gastrointestinal tract, leading to faster absorption and quicker onset of action. This feature makes them particularly suitable for conditions requiring prompt pain relief, such as musculoskeletal pain and tension headaches.[2]Paracetamol (acetaminophen) is a widely recognized analgesic and antipyretic known for its ability to relieve mild to moderate pain and reduce fever. It primarily functions by inhibiting prostaglandin synthesis in the central nervous system.[3] However, its effectiveness in treating muscle pain can be further enhanced when paired with a muscle relaxant like Orphenadrine citrate.[4]

Orphenadrine citrate is a centrally acting skeletal muscle relaxant with additional analgesic properties. It helps relieve muscle spasms and discomfort by blocking NMDA receptors and muscarinic pathways, leading to improved pain management. When combined with paracetamol, it provides comprehensive relief by targeting both nociceptive and muscular components of pain.[5]

The formulation of immediate-release tablets containing paracetamol and Orphenadrine citrate aims to deliver rapid therapeutic effects, ensuring efficient pain relief and improved patient compliance. The development process involves selecting appropriate excipients, optimizing tablet characteristics, and assessing key parameters such as disintegration time, dissolution profile, and bioavailability. Achieving a stable and effective formulation requires careful consideration of manufacturing feasibility and regulatory standards.[6] Immediate release tablets provide rapid onset of action, increase bioavailability, cost-effective, ease of swallowing, better patient compliance, immediate therapeutic effect.

Current technologies in oral drug delivery

Controlled-Release (CR) Preparations

CRtechnologies for oral drug delivery comprises diffusion-controlled, chemically controlled systems, and solvent-activated. Diffusion-controlled systems depend on drug diffusion through a polymer matrix or membrane. Osmotic control or polymer swelling is used in solvent-activated systems. Drug release via cleavage from polymer chain or polymer degradation occurs in chemically controlled systems.

Targeted-Release Preparations

This targeted release preparation confirms drug release at a specific location in GI tract. Localization to the oral cavity and rectum is relatively simple, but longitudinal and lateral limitations are required to achieve targeted gastric delivery in the small and large intestines.

Immediate-Release (IR) Preparations

This preparation is design for quick onset of action, particularly for coronary vasodilators, antipyretics and analgesics. Through transmucosal absorption they enhance bioavailabilty, making them ideal for elderly or bedridden patients, dysphagic. Conventional IR forms comprises utilizing effervescent mixtures (e.g., sodium bicarbonate + citric acid), superdisintegrants (e.g., sodium starch glycolate, croscarmellose sodium, crospovidone), and fast-disintegrating tablets.

Criteria for Immediate-Release Drug Delivery Systems

IR dosage forms should:

- Disintegrate and dissolve speedily in the stomach (solid forms)
- better taste masking (liquid forms)
- Non-fragile, portable, and leave minimal residue.
- Have a good mouth feel and less sensitivity to environmental conditions
- Be manufacturable using cost-effective processes and conventional.

Advantages of Immediate-Release Drug Delivery Systems

- Improved patient convenience and compliance.
- Enhanced dose flexibility and stability.
- Helps in controlled/sustained release activities.
- Permits great amount of drug loading in a solid form
- Adaptable to existing packaging processes and manufacturing.
- Remove dose-dumping risks
- Helpful in both early and late disease stage.

Drug Profile:

1. Paracetamol (Acetaminophen)

- **Molecular Formula**: C8H9NO2
- **Molecular Weight**: 151.16
- **Category**: Analgesic
- **Description**: Non-hygroscopic white powder and Odourless.
- **Solubility**: Very slightly soluble in cold water; more soluble in hot water
- **Log** P: 0.91
- **pKa**: 9.86 (Acidic), -4.4 (Basic)

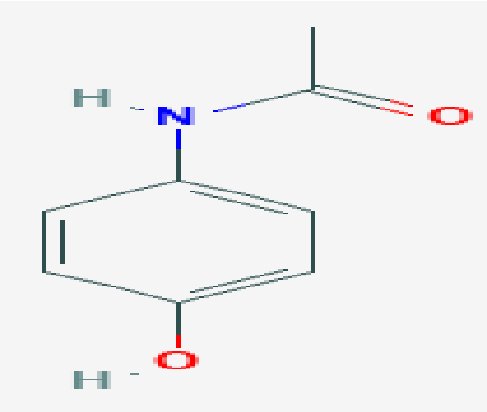


Figure 1: Paracetamol (Acetaminophen)

Mechanism of Action
Paracetamol is often classified as an NSAID, but its more accurate mechanism is not fully understood. It inhibits cyclooxygenase (COX) enzymes and blocks COX-3, a variant of COX-1 and COX-2. It relieves pain by increasing the pain threshold and acting on the heat-loving center of the brain to reduce fever

Pharmacodynamics:
Shows antipyretic and analgesic effects, but have no anti-inflammatory properties. It does not affect platelet aggregation, acid-base balance and uric acid secretion.

Pharmacokinetics:
- Absorption: shows 88% oral bioavailability and peak plasma concentration in 90 minutes
- Distribution: 10-20% binds to RBCs and Volume of distribution is 0.9 L/kg
- Metabolism: Metabolism occurs in liver by the conjugation and cytochrome P450 enzyme pathway (CYP2E1) to form a reactive metabolite called NAPQI. NAPQI can deplete glutathione and cause liver toxicity at higher dose.
- Elimination: Excreted in urine: In 24 hrs. 90% of the dose is excreted
- Half-life: 2.5 hours (normal), 4–8 hours (overdose)

Indications:
Used as fever reduction, mild to moderate pain and for severe pain management.

Adverse Effects:
Lower toxicity is detected at therapeutic dose. Overdose may leads to cause renal tubular necrosis, hypoglycemic coma, liver failure and toxicity. N-acetylcysteine an antidote can avoid liver damage if administered early.

Drug Interactions:
Avoid alcohol, as it increases the risk of hepatotoxicity. Food does not affect absorption. [23]

2. Orphenadrine
- **Molecular Formula**: C18H23NO
- **Molecular Weight**: 461.5 gm/mol
- **Category:** Skeletal Muscle Relaxant
- **Description:** Odourless, non-hygroscopic white powder
- **Solubility:** Sparingly soluble in water, slightly soluble in alcohol

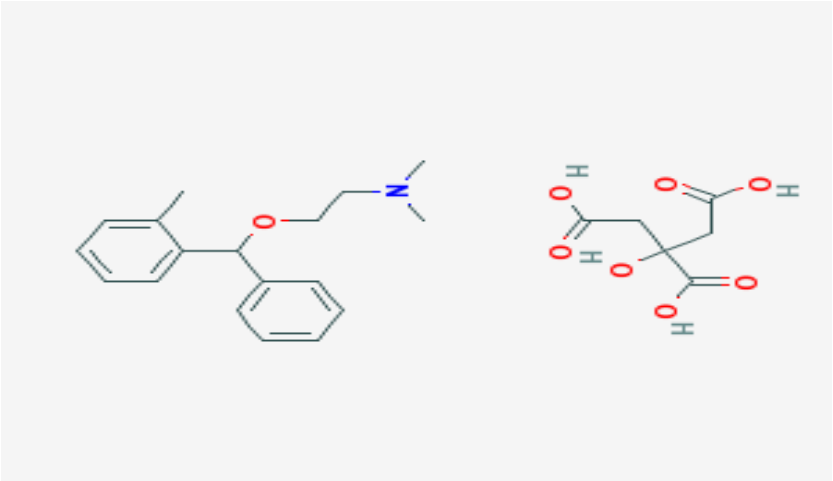


Figure 2: Orphenadrine

Pharmacodynamics:
Orphenadrine is used as an additional therapy for musculoskeletal pain and symptoms by reducing muscle convulsions without directly affecting muscle tone. It has central anticholinergic, mild antihistamines and local anesthetic properties, making it effective in relieving pain and improving mobility.
Additionally, orphenadrine plays a role in treating symptoms of Parkinson's disease, particularly rigidity and tremor. This ensures that the balance between cholinergic and dopaminergic neurotransmission is restored in the basal ganglia. Modulation of neurotransmitter activity improves spontaneous motor control and reduces muscle stiffness associated with neurological diseases.

Mechanism of Action:
Orphenadrine blocks histamine H1 and NMDA receptors, reducing the perception of pain and neuromuscular hyperactivity. By inhibiting the effect of acetylcholine, it counteracts excessive stimulation of the cholinergic system, leading to improved muscle relexation and control of movement. This inhibition can help treat diseases such as muscle cramps, parkinson's symptoms, and tension headaches.

The anticholinergic effect of orphenadrine also contributes to mood levels. This is advantageous for patients with chronic pain or symptoms. Furthermore, its mild anaesthesia improves the muscle arm and the ability Orphenadrine blocks histamine ability to relieve the neurological symptoms themselves.[24]

Pharmacokinetics:

- Absorption: Nearly completely absorbed in the gastrointestinal tract
- Metabolism: Metabolism occurs in liver and form active metabolites N,N-didemethylorphenadrine and N-demethylorphenadrine
- Half-life: 13–20 hour.

Materials and Methods
Collection of material: Paracetamol and Orphenadrine Citrate drugs are purchased from the suppliers and other materials are procured by the institute.

Formulation Development

Ingredients	A	B	C	D
DryMixing				
Paracetamol	450	450	450	450
OrphenadrineCitrate	35	35	35	35
MaizeStarch	84	78	69	63
BINDERADDITION				
Povidone(PVPK-30)	15	15	30	30
Water	**Qs**	**Qs**	**Qs**	**Qs**
EXTRAGRANULATION				
SodiumStarchGlycollate	6	12	6	12
LUBRICATION				
Magnesium Stearate	3	3	3	3
ColloidalAnhydrousSilica	1	1	1	1
PurifiedTalc	6	6	6	6

Table 1: Composition of immediate release tablet

Procedure
A quantity of Paracetamol and Orphenadrine Citrate is given in the formulation table. Both the ingredients are sifted from 80 #. Quantity of Maize Starch is sifted through 100#. All the sifted material mixed by using Rapid Mixer Granulator for 10 minutes at 150rpm. Binder solution is prepared by dissolving required quantities. Wet mass received from the RMG and sifted using sieve10#.

In tray dryer above mass was dried for 30 minutes at 55 ºC till the wanted LOD was achieved i.e., NMT 3%. And for sizing pass through 16 #. Take the granules and add SSG sifted from 40# in octagonal blender to mix it well. All lubricating agents (Magnesiumstearate, Colloidal Anhydrous Silica, Purified Talc) are sifted through 40# and for 10mins. blend with dried granules. Now, final blend was subjected to compression using12.70mmBevelledgeground punch with break line on upper side.

Evaluation Parameters
A. Preformulation Studies
An organoleptic property of Paracetamol and Orphenadrine Citrate is observed by using sensory organs and melting point of the drugs is measured by using melting point apparatus shown in the following table no 2.

Table 2: Organolepticproperties and melting point of drugsamples

Drug	Parameter	Observation Result
Paracetamol	Colour	White
	Odour	Odourless
	Melting Point	169-170ºC
Orphenadrine citrate	Colour	White
	Odour	Odourless
	Melting Point	132-133ºC

- **Drug Excipient Compatibility Study**

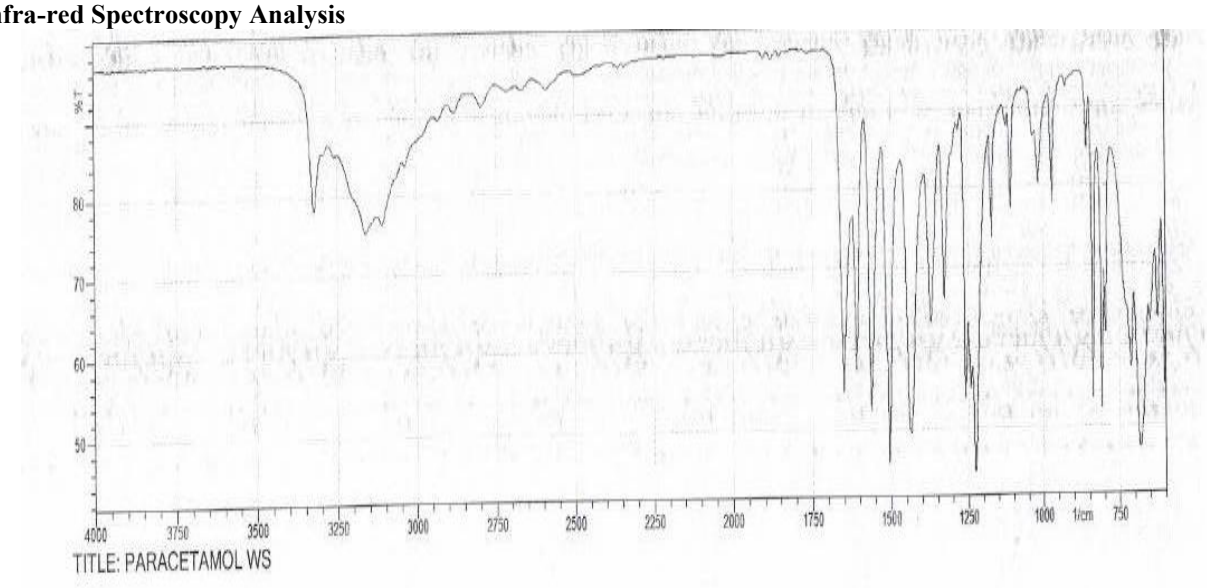
Preliminary Analysis: -Drug Excipients incompatibility study performed by using stability chamber which is used for storage of products for certain periods of time in specified temperature and RH control. After then IR spectroscopy is used therefore the inspection of degradation and chemical change is done.

Table 3: Drug excipient compatibility study

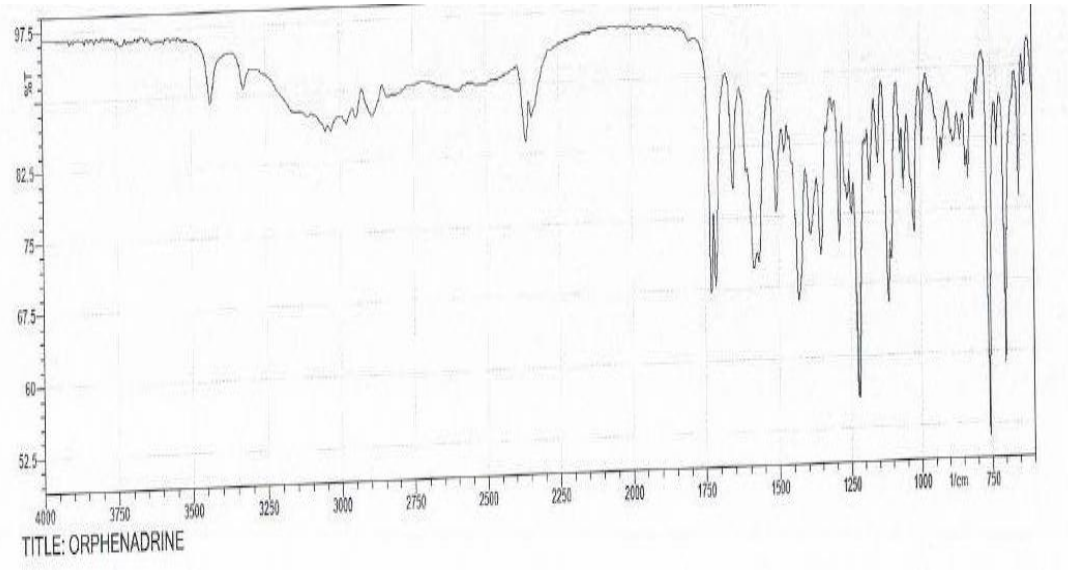
Ingredient	Ratio	Initial	Condition			
			30°C/65% RH (RealTime)		40°C/75% RH (Accelerated)	
			15 days	1 month	15 days	1 month
Orphenadrine Citrate	NA	white powder	NCC	NCC	NCC	NCC
Paracetamol	NA	white powder	NCC	NCC	NCC	NCC
Paracetamol+ PVPK-30	1:1	white powder	NCC	NCC	NCC	NCC
Paracetamol+ Maize Starch	1:1	Offwhite powder	NCC	NCC	NCC	NCC
Paracetamol+SSG	1:1	White powder	NCC	NCC	NCC	NCC
OrphenadrineCitrate+PVPK-30	1:1	White powder	NCC	NCC	NCC	NCC
OrphenadrineCitrate+Maize Starch	1:1	Offwhite powder	NCC	NCC	NCC	NCC
OrphenadrineCitrate+SSG	1:1	White powder	NCC	NCC	NCC	NCC
Paracetamol + Orphenadrine Citrate+all excipients	1:1:1	White Powder	NCC	NCC	NCC	NCC

Note- NCC (No conformational change) in physical appearance from initial description, RH (Relative Humidity).
It can be seen from the above data that Orphenadrine Citrate & Paracetamol combination is stable with all the excipients used for formulation and development.

Infra-red Spectroscopy Analysis



Graph 1: IR Spectroscopy of Paracetamol



Graph 2: IR Spectroscopy of Orphenadrine Citrate

B. Pre-compression and Post-compression parameters

The powder blend and final tablets from all batches were subjected to rigorous evaluation to ensure quality, uniformity, and compliance with regulatory standards. Pre-compression parameters such as loss on drying, bulk density, tapped density, and compressibility index were assessed to determine the blend's flow properties and suitability for compression. These tests help predict potential issues during tablet manufacturing, such as poor flowability, segregation, or compaction problems.

Similarly, post-compression parameters like appearance, weight variation, hardness, and friability, assay, disintegration, and dissolution tests were conducted to confirm the final product's mechanical strength, uniformity, and drug release profile. These tests are essential to ensure that the tablets meet pharmacopeial specifications, remain stable during storage, and provide consistent therapeutic effects upon administration.

Table 4: Pre-compression parameters

Trial	Bulk density (gm/ml) SD n = 3	Tapped density (gm/ml) SDn = 3	Angleof repose SDn = 3	Hausner's ratio	C.I (%)	LOD (%)
A	0.540±0.01	0.666±0.01	30.54±0.06 (excellent)	1.23 (Fair)	18.90 (Fair)	1.10
B	0.500±0.04	0.625±0.02	32.00±0.03 (Good)	1.25 (Fair)	20.00 (Fair)	1.28
C	0.430±0.06	0.550±0.01	36.24±0.07 (Fair)	1.27 (Passable)	21.80 (Passable)	1.06
D	0.476±0.02	0.571±0.01	34.41±0.01 (Good)	1.19 (Fair)	16.60 (Fair)	0.96

From flow property of the lubricated blend **C** showed passable flow property, **B & D** showed fair flow properties and **A** showed good flow ability.

Post Compression parameters:-

Batch **C** & **B** showed capping after compression while Batch **A** & **D** were well within the limits.

- **Appearance**: The tablets from all trial batches were white round shaped with having break line on upper side and plain on other side.
- **Weight variation**: The percent deviation in weight variation from average values for all the batches were within limits (NMT 5%).
- **Thickness:** The thickness of tablets was found to be within limit of deviation from average value (NMT 5%)
- **Hardness:** The hardness of core tablets was found to be ranging from 1.72kg/cm^2 to 11.50 kg/cm^2. Batch **A** showed highest hardness, while batch **B** showed lowest.
- **Friability:** The friability of tablets was less than 1% only for batch **A** & **D** which indicated good handling and transportation characteristics. While batch B & C showed capping.
- **Disintegration:** As the concentration of the super-disintegrant increased the disintegration time decreased. The selected batch A showed disintegration time of 2.18 -2.25 mins.

- **Assay:** The assay was found to be between 97-103 % which was under specified limit. Among all the formulations A showed maximum drug release within 35 minutes and was compared with the dissolution profile of Marketed Formulation.

Table 5: Post compression parameters table

Trials	Weight (mg)SD n=3	Thickness (mm) SDn=3	Diameter (mm)SD n=3	Hardness (N) SD n=3	Friability (%)	D. T.	Assay (%)	
							Paracetamol	Orphenadrine Citrate
A	601.15±5.07 mg	4.27±0.038 mm	12.79±0.001 mm	11.00±0.50 kg/cm^2	0.21%	2 min 18 sec- 2 min 25 sec.	98.75 %	97.86 %
B	600.8±5.61 mg	4.29±0.037 mm	12.78±0.003 mm	2.50±0.78Kg/cm^2	4.25% (Capping)	1 min 06 sec- 1 min 15 sec	98.19%	97.21%
C	607.6±13.08 mg	4.36±0.055 mm	12.79±0.002 mm	4.50±0.56 Kg/cm^2	4.65% (Capping)	2min 50sec- 3 min 05sec	97.56%	97.00%
D	599.7±5.07 mg	4.31±0.044 mm	12.78±0.002 mm	5.50±0.45 Kg/cm^2	0.46%	2 min 12sec- 2 min 19sec	98.13%	97.81%

Design of Experiments

Layout of Actual Design of DOE

The Box-Behnken design, incorporated into Design Expert software version 13, was utilized for optimization studies to evaluate the influence of independent variables on dependent variables. The study followed the principles of Design of Experiments (DoE), leading to the recommendation of 15 experimental runs. The outcomes of these experiments are summarized in table no. 6. Immediate release tablets were formulated and analyzed, with a primary focus on key dependent variables, including hardness (R1), disintegration time (R2), and friability (R3). The experimental results provided valuable insights into the interactions between different formulation factors and their impact on tablet characteristics. Based on the findings, an optimized formulation was developed by considering both independent and dependent variables identified during the trials. This systematic approach ensured that the tablets achieved the desired specifications for hardness, disintegration time, and friability. The application of the Box-Behnken design enabled an efficient and structured evaluation of formulation parameters, ultimately leading to the successful optimization of the immediate-release tablet formulation.

Table 6: Design of experiments

Std.	Run	Factor1 A: Disintegrants	Factor 2 B: Binder	Response 1 Hardness Kg/cm^2	Response 2 Dt. Min.	Response 3 Friability %
14	1	12	30	5	2.1	0.1
2	2	6	15	11	2.2	0.08
1	3	6	15	12	2.23	0.08
16	4	12	30	5	2.13	0.1
10	5	6	30	3	2.5	4.5
13	6	12	30	6	2.1	0.1
8	7	12	15	2	1.18	4.2
15	8	12	30	6	2.11	0.1
11	9	6	30	4	3	4.6
3	10	6	15	11	2.25	0.07
7	11	12	15	2.5	1.15	4.2
6	12	12	15	2	1.2	4.3
9	13	6	30	3	3	4.5
12	14	6	30	4	3.1	4.5
5	15	12	15	2.5	1.19	4.3
4	16	6	15	11	2.2	0.04

Response 1: Hardness

Table 7: ANOVA Hardness Table

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	190.25	3	63.42	253.67	<0.0001
A-disintegrant	49.00	1	49.00	196.00	<0.0001
B-binder	20.25	1	20.25	81.00	<0.0001
AB	121.00	1	121.00	484.00	<0.0001
Pure Error	3.00	12	0.2500		
Core Total	193.25	15			

Response 2: Disintegration Time

Table 8: Disintegration time

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	5.94	2	2.97	134.88	<0.0001
A-disintegrant	3.35	1	3.35	152.06	<0.0001
B-binder	2.59	1	2.59	117.70	<0.0001
Residual	0.2863	13	0.0220		
Lack of Fit	0.0625	1	0.0625	3.35	0.0921
Pure Error	0.2238	12	0.0186		
Core Total	6.23	15			

Summary & Conclusion

- The aim of the present investigation was to formulate and evaluate immediate release tablets of or phen adrinecitrate and paracetamol by wet granulation method.
- The drug & excipients used did not show any incompatibilities as interpreted from drug-excipient compatibility studies.
- The formulations were evaluated for pre-compression and post-compression characteristics and showed satisfactory results.
- Based on the findings on various laboratory trials and evaluations, batch **A** met set desired quality target product profile (QTPP) of the finished product.
- Following excipients were finalized for final formulation.

Maize Starch (7%) finalized as diluent, PVPK-30 (2.5%) as a binder, Sodium Starch Glycollate (1%) as a super-disintegrant, Maize Starch (7%) as an extra granular disintegrant + lubricant, Aerosil (0.16%) as a glidant, Magnesium stearate (0.5%), and Purified Talc (1%) as a lubricant.

From the results obtained, following conclusion was drawn:

1. The drug excipient compatibility studies showed that excipients used in the final formulation did not show any interaction with the drug. The excipients were compatible with the both the drugs.
2. Pre-compression and post compression parameters were mechanically stable and complied with the pharmacopoeial specifications.
3. In-vitro release study showed that the formulation A showed good release because of rapid disintegration of tablet.
4. Based on release profile of different formulation A showed the maximum of 99.34

% of paracetamol and 98.81% of Orphenadrine Citrate and was compared with the marketed formulation.

References

1. Atram SC. Formulation and evaluation of immediate release tablet using response surface methodology. Asian Journal of Pharmaceutics. 2011;5:1-10.
2. Sekar V, Chellan VR. Immediate release tablets of telmisartan using superdisintegrant-formulation, evaluation and stability studies. Chemical and Pharmaceutical Bulletin. 2008 Apr 1;56:575-7.
3. Behera S, Ghanty S, Ahmad F, Santra S, Banerjee S. UV-visible spectrophotometric method development and validation of assay of paracetamol tablet formulation. Journal of Analytical & Bioanalytical Techniques. 2012 Oct 31;3:151-7.
4. Jumaa AK, Abdulrasool AA. Formulation and Clinical Evaluation of Orphenadrine citrate as a Plain Tablet. Iraqi Journal of Pharmaceutical Sciences. 2006;15:1-9.
5. Imtiaz Z, Kanwal A, Akram I, Latif K. Formulation of extended release orphenadrine citrate tablets to treat muscle spasm and pain. Journal of Contemporary Pharmacy. 2020;4:30-3.
6. Pathak N, Kumar A, Methkar V, Pant P, Rao RT. Formulation and optimization of immediate release tablet of an antialcohlic drug by dry granulation method. Cellulose. 2011;90:60.

7. Raymond C Rowe, Paul J Sheskey and Marian E Quinn, 'Handbook of Pharmaceutical Exicipients". 6th Edition: 185, 404, 581, 663, 685, 728.
8. Jawa Ghazanfar Ali, Islam Muhammad, Saeed Hamid, Muhammad Ali A, Hakeem Shoaib and Samiyah Tasleem,; Simultaneous Determination and Quantification of Paracetamol, Caffeine and Orphenadrine Citrate using Stability Indicating HPLC Method in a Fixed Dose Combination Tablet Dosage Form, Annals of Pharmacology and Pharmaceutics. 2020;5:1185-95.