ORIGINAL PAPER

FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLET OF PARACETAMOL AND ORPHENADRINE CITRATE BY DIRECT COMPRESSION METHOD

BHARAT ASHOK NIKAM[1], AMOL U. GAYKE[1,*]

Manuscript received: 22.06.2022; Accepted paper10.09.2022;
Published online: 30.09.2022.

Abstract. *The objective of this research work was to formulate, develop and evaluate immediate release tablet of paracetamol and orphenadrine citrate by direct compression method. Paracetamol which is antipyretic and orphenadrine citrate is skeletal muscle relaxant. The drug paracetamol and orphenadrine citrate was taken and formulated with different concentration of cross-povidone, mannitol, micro-crystalline cellulose, magnesium stearate and talc. Where cross-povidone as a superdisintegrant, mannitol as diluent, micro-crystalline cellulose as binder, magnesium stearate as lubricant and talc as a glidant used. the preformulation parameters such as bulk density, tapped density, compressibility index and hausner's ratio were analysed. The thickness, hardness, friability, weight variation, disintegration time & drug content uniformity was evaluated. the in-vitro drug release studied were performed in the usp type (ii) paddle using 0.1N HCl as a dissolution media at 75 rpm speed and temperature of 37±0.5ºC. The % drug release at different time interval was estimated using UV method. Based on the evaluation result f9 trial was selected as the best formulation. The in-vitro drug release profile of the drugs was compared with marketed reference product. All the evaluated result was found to be satisfied with the reference products.*

Keywords: *Paracetamol; orphenadrine citrate; direct compression.*

1. INTRODUCTION

For decades, oral drug delivery has been recognised as the most widely used route of administration among all the routes that have been investigated for the systemic delivery of drugs via various pharmaceutical products in various dosage forms. The oral route's popularity may be due in part to its ease of administration, as well as the traditional belief that the drug is well absorbed along with the gastrointestinal tract and food stuff when administered orally. It is the most desirable and preferred method of administering therapeutic agents for their systemic effects. Furthermore, oral medication is widely regarded as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, owing to patient acceptance, ease of administration, and a cost-effective manufacturing process [1-3].

On the other hand, pharmaceutical dosage forms such as tablets, capsules, suppositories, creams, ointments, liquids, aerosols, and injectables have been used to deliver drugs to patients for the treatment of a variety of diseases. Even today, conventional dosage forms are the most common pharmaceutical vehicles in the prescription and over-the-counter

[1]Jagdamba Education Society, S.N.D. College of Pharmacy, Babhulgaon Tal, 423401 Maharashtra, India.
[*] *Corresponding author: amolgayke6687@gmail.com.*

drug markets. The oral conventional types of dosage form are known to provide a rapid release of drug [4]. Any technology's success is determined by the ease with which it can be manufactured and by its desirable biopharmaceutical Properties. The fundamental goal of drug therapy is to produce a therapeutic effect. Almost 90% of all drugs used to produce systemic effects are administered orally [5]. Tablet drug delivery systems can range from simple immediate release (IR) dosage forms to complex extended or modified release dosage forms. An important variable in any solid dosage form is the rate at which the active substance enters solution or dissolves to reach the systemic circulation. The dissolution of the active substance is required for it to be absorbed through biological membranes into systemic circulation and elicit the desired pharmacological activity [6-7]. The most important role of a drug delivery system is to get the drug "delivered" to the site of action in sufficient quantity and at the appropriate Rate [8-9]. Tablets are solid pharmaceutical dosage forms that contain drug substances with or without appropriate diluents and are prepared by compression or moulding methods. They have been in widespread use since the late nineteenth century, and their popularity continues to grow. Tablets remain popular as a dosage form due to the benefits they provide to both the manufacturer and the patient [10].

Although tablets are most commonly discoid in shape, they can also be round, oval, oblong, cylindrical, or triangular. They can vary greatly in size and weight depending on the amount of drug substance present and the Intended Method of Administration [11].

2. MATERIALSAND METHOD

2.1. PRE-FORMULATION STUDIES

Pre-formulation studies are performed to investigate the physical and chemical properties of active pharmaceutical ingredients and in combination with other substances such as excipients. It is the initial step towards reasonable dosage form creation. Pre-formulation may be described as a phase of R&D where a scientist characterizes the physicochemical properties of a drug substance, in order to develop safe, effective and stable dosage form.

2.2. ORGANOLEPTIC PROPERTIES

a. **Colour:** A little amount of Paracetamol and Orphenadrine citrate were separately taken in butter paper and examined under well lighted area.
b. **Odour:** Small amount of Paracetamol and Orphenadrine citrate samples were smelled to get the odour.
c. **Appearance:** A pinch of Paracetamol and Orphenadrine citrate were taken between two fingers and appearance was observed.

2.2.1. Determination of melting point

Melting point is the first indication of purity of the sample. Melting point of paracetamol and orphenadrine citrate were performed separately by open capillary method. APIs was taken in a glass capillary whose one end was sealed by flame. The capillary was

then dipped into the liquid paraffin, placed inside the melting point apparatus and melting point was noted.

2.2.2. Solubility study

The solubility of paracetamol and orphenadrine citrate were determine in various solvents (i.e., methanol, 0.1N hydrochloric acid, phosphate buffer 6.8 and water) pH separately. In a test tube 10 mL of required solvent was transferred and 20 mg of each API was added. The mixture was then sonicated for 10 min and observation was done for the particles remain if any.

2.3. UV-VISIBLE SPECTROPHOTOMETRIC ANALYSIS

All reagents were of analytical grade and 0.1N hydrochloric acid was used as solvent to prepare dilution.10 mg of API was dissolved in 10 mL of solvent (0.1N hydrochloric acid) to produc e 1000 µg/mL. From this prepared solution 0.2 mL of sample was taken and further diluted with solvent (0.1N hydrochloric acid) up to 10 mL to produce 20 µg/mL sample and spectra was observed.

Orphenadrine citrate: 10 mg of API was dissolved in 10 mL of solvent (0.1N hydrochloric acid) to produce 1000 µg/mL. From this prepared solution 1 mL of sample was taken and further diluted with solvent (0.1N hydrochloric acid) upto 10 mL to produce 100 µg/mL sample and spectra was observed.

The UV spectra of paracetamol and orphenadrine citrate were investigated. The analysis was performed using V550 spectrophotometer (JASCO Corp, Tokyo, Japan). Glassware used were rinsed thoroughly with doubled distilled water and dried.

2.4. CALIBRATION CURVE OF PARACETAMOL IN 0.1N HYDROCHLORIC ACID

Stock solution was prepared as follows: 10 mg of paracetamol was dissolved in 10 mL of solvent (0.1N hydrochloric acid) to produce 1000 µg/mL. In addition, solution A was prepared from stock solution 1 mL of sample was withdrawn and diluted upto 10 mL with solvent (0.1N hydrochloric acid) to produce 100 µg/mL. Finally, from solution A, different volums, such as 0.5, 1.0, 1.5, 2.0 and 2.5 mL were withdrawn and diluted up to 10 mL with solvent (i.e., 0.1N hydrochloric acid) to obtain 5.0, 10.0, 15.0, 20.0 and 25.0 ppm concentrations and, then, the absorbances were measured at 243 nm, by UV-Vis spectrophotometry.

2.5. CALIBRATION CURVE OF ORPHENADRINE CITRATE IN 0.1N HYDROCLORIC ACID

Stock solution was prepared such as: 10 mg of orphenadrine citrate was dissolved in 10 mL of solvent (i.e., 0.1N hydrochloric acid) to produce 1000 µg/mL. Solution A was obtained from stock solution: 1 mL of sample was withdrawn and diluted upto 10 mL with solvent (0.1N hydrochloric acid) to produce 100 µg/mL. From solution A 0.5, 1.0, 1.5, 2.0

and 2.5 mL were withdrawn and diluted up to 10 mL with 0.1N hydrochloric acid to obtain 5.0, 10.0, 15.0, 20.0 and 25.0 ppm concentrations, and absorbances were measured at 212 nm.

2.6. FTIR OF PARACETAMOL

The IR spectra of paracetamol and orphenadrine citrate were recorded using IRAffinity-1S Fourier Transform Infrared spectrophotometer (Shimadzu, Japan). Spectrum was recorded by using potassium bromide (KBr) as blank, at a resolution of 4 cm over a range 400-4000 cm^{-1}. The peaks in the spectrum of paracetamol and orphenadrine citrate were compared with the principle peaks of the IR spectrum reported in the monograph [15].

2.7. DRUG EXCIPIENT COMPATIBILITY STUDY

Drug excipient compatibility studies represent an important phase in drug development. Before a drug substance is formulated into a desired dosage form, there is need for the formulator to fully consider the chemical structure of the drug substance, type of delivery system required and the proposed manufacturing process. Drug substances are usually combined with the excipients which serve different and specialized purpose (Table 1). Excipients are pharmacologically inert, but given the right conditions they can undergo chemical reactions and physical interactions with medicinal molecules under favorable environmental conditions. Compatibility test on drug excipient have been used to approve or reject excipients for use in pharmaceutical formulation. The API alone and with individual excipients were taken in different ratios and mixed well. Passed through sieve, the blend was filled into the glass vials and kept in wet and dry conditions to 40± 2°C/75 ± 5% RH and 30 ± 2ºC/ 60 ± 5% RH.

Table 1. Drug–Excipient Compatibility Study Ratio

No.	Sample	Ratio
1	Para + Orphenadrine : Cross povidone	1:1
2	Para + Orphenadrine: Microcrystalline cellulose	1:1
3	Para + Orphenadrine: Mannitol	1:1
4	Para + Orphenadrine: Magnesium stearate	1:1
5	Para + Orphenadrine: Talc	1:1

2.8. FACTORIAL DESIGN MODEL

In order to formulate stable Immediate Release tablet, 3^2 full factorial design was applied to the formulation that showed the satisfactory results to see the effect of varying the concentrations of variables such as Cross povidone (X1) and Microcrystalline cellulose (X2) on responses like disintegration time and hardness (Table 2). The levels of two factors were selected on the basis of studies carried out before implementing the experimental design.

Tables 2 and 3 summarizes the experimental runs, their factor combinations and the translation of the coded levels to the experimental units used in the study [15].

Table 2. Factorial design model parameters

Independent variables	Name	Unit	Levels		
			Low (-1)	Middle (0)	High (+1)
X1	Cross povidone	%	4.0	5.0	6.0
X2	Microcrystalline cellulose	%	5.0	7.5	10.0

Table 3. Formulation strategy

No.	Ingredients	Quantity [mg]								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Paracetamol	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0	450.0
2.	Orphenadrine Citrate	35.0	35.0	35.0	35.0	35.0	35.0	35.0	35.0	35.0
3.	Cross povidone	26.0	26.0	26.0	32.5	32.5	32.5	39.0	39.0	39.0
4.	MCC	32.5	48.7	65.0	32.5	48.7	65.0	32.5	48.7	65.0
5.	Mannitol	93.5	77.3	61.0	87.0	70.8	54.5	80.5	64.3	48.0
6.	Magnesium stearate	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
7.	Talc	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Total weight of tablet		650 mg								

2.9. EVALUATION PROCEDURES

2.9.1. Pre-compression parameter [16]

Bulk Density. Powder blend was accurately weighed & passed through sieve # 80 and was carefully poured into 100 mL graduated cylinder. The capacity was calculated as mL using the graduation marking on cylinder. Bulk density is an essential parameter used to determine occupancy in blender or hopper or capsule filler etc.

Tapped Density. After measuring the bulk volume, the same measuring cylinder containing the powder blend was set into tap density apparatus and was mechanically tapped, allowing it to drop under its own weight that provides a fixed drop from 14±2 mm. The tap density apparatus was run for 500 taps volume was recorded as (Vb). The following formula is used to determine tapped density.

$$\rho t = m/Vt$$

where, ρt is tapped density; m is mass of powder; Vt is tapped volume of powder.

Tapped Density represents dense packing. Regularly shaped particles (spheres) have a greater tapped density value than irregularly shaped particles (needles).

Flow Properties. Flow assessment of API and excipients made to ensure that the powder will flow adequately through processing equipment's such as compactor, hopper or tablet press. Poor flow ability can lead to tablet weight variation due to in ability to feed powder into die.

Compressibility index (C.I.) is the measure of propensity of a powder to consolidate. It is the measure of inter particulate interaction in free-flowing powder, such interaction is generally less significant and BD and TD value will be close. For poor flowing material it causes frequently greater inter particle interaction, bridging between particles often results in

lower bulk density and greater difference between BD and TD and this difference is reflected in compressibility index.

$$C.I\ (\%) = (\rho t - \rho b)/\ \rho t \cdot 100$$

where, ρt is tapped density and ρb is bulk density.

Table 4. Standard values for Compressibility index

Compressibility Index [%]	Flow Character
≤ 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
> 30	Very very poor

Hausner's ratio is a measurement used to describe the compressibility of powder. It is the ratio of tapped density to bulk density (Table 5). It is calculated by the formula

$$\text{Hausner's Ratio} = \rho t/\rho b$$

where, ρt is tapped density and ρb is bulk density.

Table 5. Standard values for Hausner's ratio

Hausner's Ratio	Flow Character
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor

Angle of Repose was determined using funnel method. To keep a coating of powder on the base an Angle of repose was created on a fixed base with a retaining lip. The base should be free of vibration. The height of the funnel was adjusted to create a symmetrical cone of powder. Care was taken to prevent vibration as the funnel was moved (Table 6). In order to minimize the impact of falling powder on the tip of the cone the funnel height was maintained approximately 2 cm from the top of the powder, by measuring the height of the powder cone and using the following equation to get the angle of repose:

$$\text{Tan}\ \theta = \text{height/radius}$$

Table 6. Standard values for Angle of repose

Angle of repose [degrees]	Flow Character
25-30	Excellent
31-35	Good
36-40	Fair – aid not needed
41-45	Passable – may hang up
46-55	Poor – must agitate, vibrate
56-65	Very poor
>66	Very very poor

2.10. POST COMPRESSION PARAMETERS

Physical appearance. The appearance of the core tablet i.e., surface texture, chipping and cracks if any were observed.

Thickness and diameter. Using vernier calipers the thickness and diameter of 10 tablets were measured during compression.

Hardness crushing strength is used to assess whether a tablet machine require a pressure modification or not. If the tablet is too hard, it may not disintegrate in time necessary to fulfil the dissolving criteria, if it is too soft it may not be able to resist packing and shipping procedures.

Friability. A total of 20 pre-weighted tablets were put in the device and subjected to rolling and repeated shock as they fall 6 inches in each rotation. After four minutes of this treatment or 100 revolutions, the tablets were weighed and the weight was compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test was considered generally acceptable and any broken or smashed tablets were not picked. The percentage friability was determined by the formula:

$$\% \text{ Friability} = (w1-w2) / w1 \cdot 100$$

where, w1 is weight of tablets before test and w2 is weight of tablets after test.

Drug content. 20 tablets were weighed to determine the mean weight and finely powdered in mortar. An amount of powered mass equivalent to 650 mg (450 mg paracetamol and 35 mg orphenadrine citrate) was accurately weighed and transferred to a 100 mL of volumetric flask 50 mL 0.1N HCl was added, and the mixture was sonicated for 15 min. The volume was made up with the remaining 50 mL of 0.1N HCl. An aliquot was filtered through 0.45µm nylon filter. The final tablet solution was further diluted with 0.1N HCl up to a concentration of 10 µg/mL and was analyzed by UV at 243 nm for paracetamol and 212 nm for orphenadrine citrate.

Weight variation. To study weight variation, 20 tablets of each formulation were weighted using electronic balance and the test was performed according to the official method. As per IP and USP not more than two tablets should differ in their average weight by more than percentages stated and no tablet must differ by more than double the relevant percentage.

Table 7. Standard values for Weight variation

No.	Average weight of tablet (IP)	Average weight of tablet (USP)	% Deviation
1	≤ 80 mg	≤ 130 mg	10
2	>80 mg – 250 mg	>130 mg – 324 mg	7.5
3	≥ 250 mg	≥ 324 mg	5

Disintegration test. In order for a medication to be absorbed from solid dosage form after oral administration, it must first be in solution and the first critical step towards this step is generally tablet disintegration. Disintegration time is an important test in immediate release

tablet. Tablet disintegration was measured using USP disintegration apparatus. Six tablets were introduced in each tube and the basket rack was placed in a beaker of water at 37 ± 2˚C. The basket assembly was moved up and down the beaker and the apparatus were operated until no residue was left. The time taken to achieve zero residue was recorded.

2.11. IN-VITRO DISSOLUTION TEST

The process of solid solute entering a solution is known as dissolution. It is defined as the quantity of drug material that enters solution per unit time under standardized circumstances of liquid/solid interface, temperature and solvent composition in the pharmaceutical business. Aliquots of dissolution media were withdrawn (10 mL) at different intervals and content of both the drugs (i.e., paracetamol and orphenadrine citrate) were measured by determining absorbance at 243 and 212 nm, respectively. 10 mL aliquot was withdrawn at the 0, 5, 10, 15, 20, 25 and 30 minutes intervals and filter by Whatman filter paper and analyzed at their respective wavelengths of UV-Vis spectrophotometer.

3. RESULT AND DISCUSSION

3.1.DRUG CHARACTERIZATION

Drug characterization parameters such as colour, odour and appearance were analysed for the procured drug samples and the results were shown in Table 8.

Table 8. Parameters for characterization of drugs.

Parameter	Paracetamol	Orphenadrine citrate
Colour	White	White
Odour	Odourless	Odourless
Appearance	Fine Powder	Fine Powder

3.2. DETERMINATION OF MELTING POINT

The melting point of paracetamol and orphenadrine citrate were determined and the results were expressed in Table 9. The observed melting point for paracetamol and orphenadrine citrate complies with reported melting points.

Table 9. Melting point of both analyzed drugs.

	Paracetamol	Orphenadrine citrate
Melting Point	167-169°C	132-134°C

3.3. SOLUBILITY STUDY

The solubility study of both the drugs was carried out by using different solvent systems as per the literature. The solubility results were shown in Table 10.

Table 10. Results for solubility study

No	Solvent	Paracetamol	Orphenadrine citrate
1.	Methanol	Soluble	Soluble
2.	0.1N Hydrochloric acid	Soluble	Soluble
3.	Phosphate buffer 6.8 pH	Soluble	Soluble
4.	Water	Soluble	Insoluble

3.5. UV-VISIBLE SPECTROPHOTOMETRIC ANALYSIS

The UV-Vis spectrophotometric analysis was used to investigate the presence of analyzed drugs from qualitative point of view. 0.1N hydrochloric acid was used as solvent system for blank as well as sample preparation for both the drugs. For paracetamol 20 µg/mL sample was used and λ max was found as 243 nm. For orphenadrine citrate 100 µg/mL samples was used and λ max was found as 212 nm. The spectra for results were expressed in Figs. 1-3.

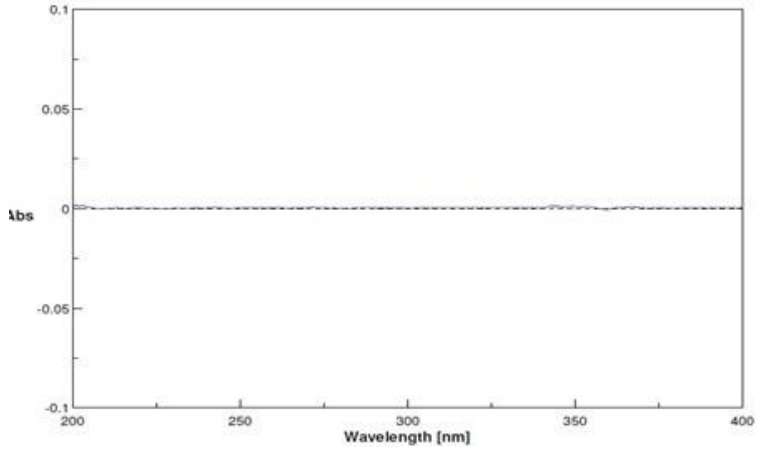

Figure 1. Blank in 0.1N hydrochloric acid.

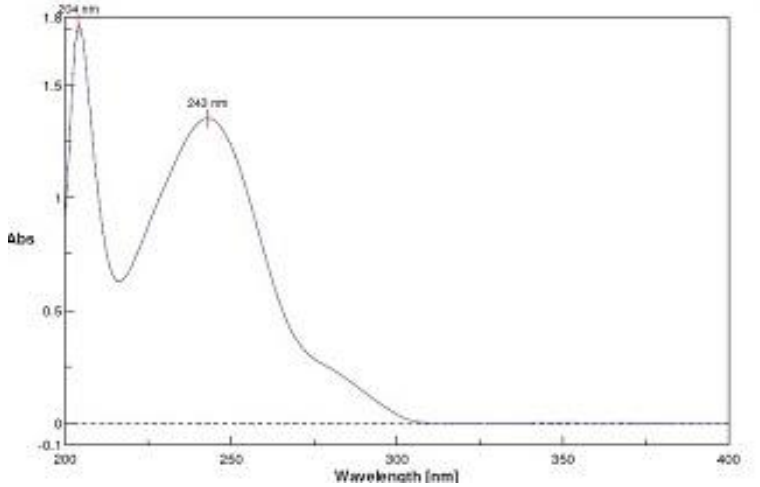

Figure 2. Paracetamol (20 µg/mL) solution in 0.1N hydrochloric acid.

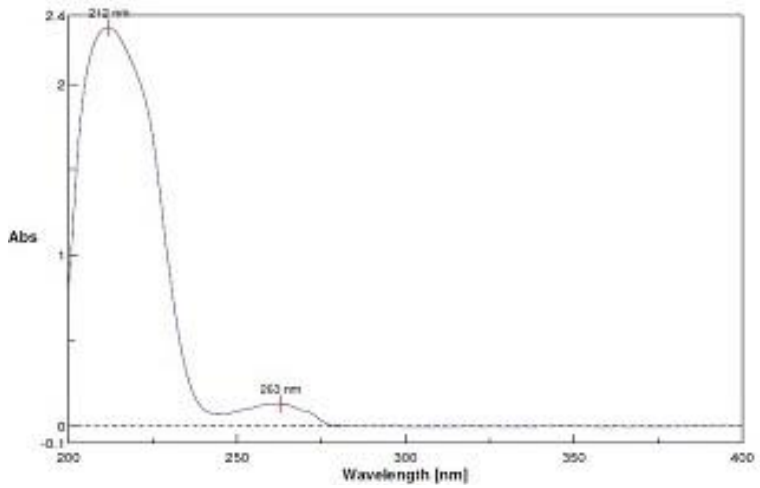

Figure 3. Orphenadrine citrate (100 µg/mL) solution in 0.1N hydrochloric acid.

3.6. PREPARATION OF CALIBRATION CURVE FOR PARACETAMOL

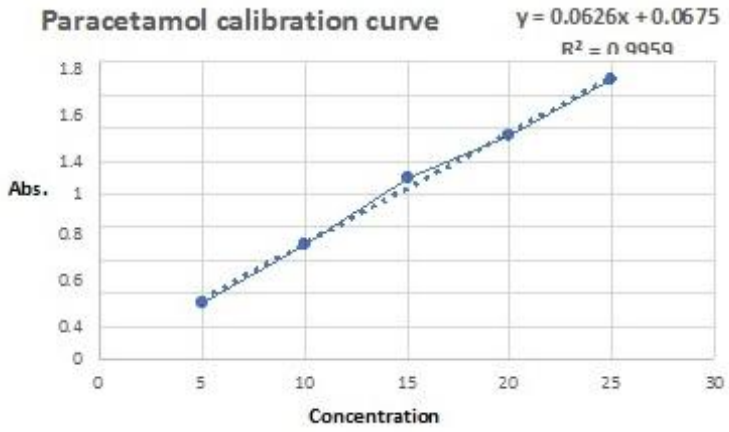

Figure 4. Calibration curve of paracetamol in 0.1N hydrochloric acid.

3.7. PREPARATION OF CALIBRATION CURVE FOR ORPHENADRINE CITRATE

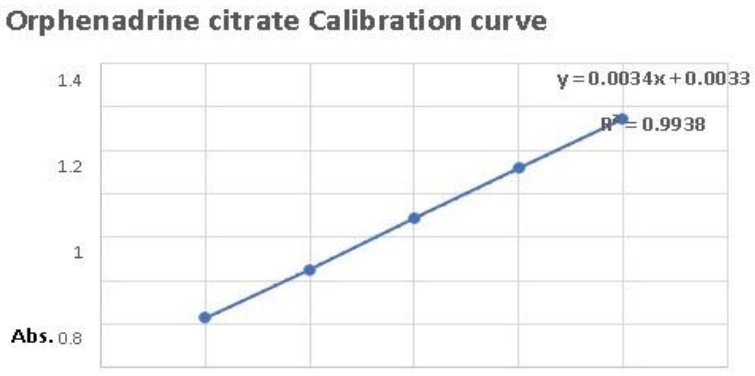

Figure 5. Calibration curve of orphenadrine citrate in 0.1N hydrochloric acid.

The calibration curves were linear for both paracetamol and orphenadrine citrate and obeyed Beer-Lambert's law in the concentration range 5-25 μg/mL. The correlation coefficient values were 0.9959 and 0.9938 indicating excellent linearity of the data.

3.8. FTIR ANALYSIS

Characteristic functional groups paracetamol were observed in FTIR spectrum according to data from Table 11 and Fig. 6.

Table 11. FTIR frequencies of paracetamol functional group

Functional group	Assigned frequency [cm^{-1}]	Reported requency [cm^{-1}]
O-H	3156.75	3200-2700
C-H stretching	2791.68	3000-2840
N-H (Secondary amine)	3321.24	3350-3310
C=C stretching	1608.69	1620-1610
C=O stretching	1767.19	1770-1780

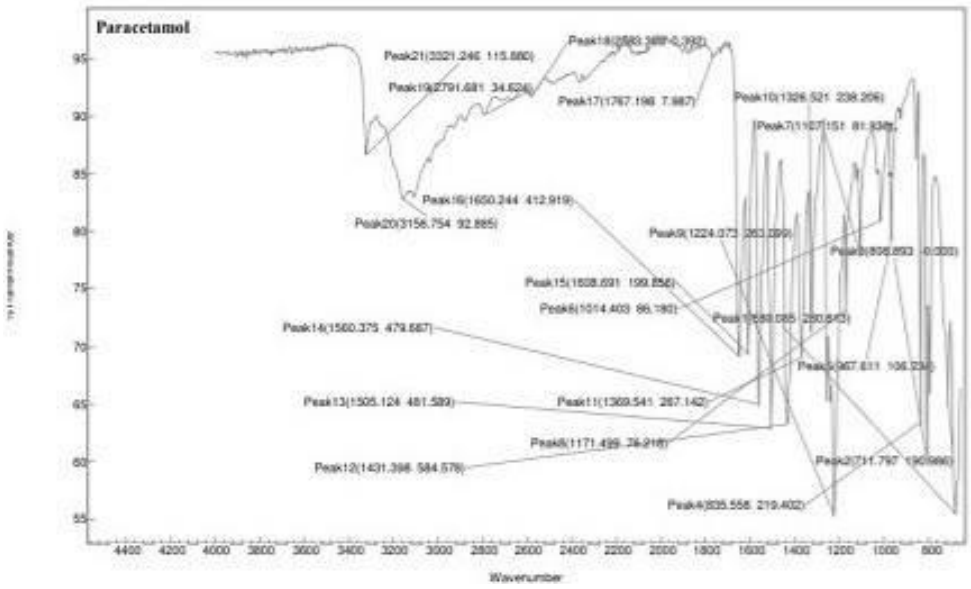

Figure 6. FTIR spectrum of paracetamol.

Characteristic functional groups of orphenadrine citrate were observed in FTIR spectrum as shown in Table 12 and Fig. 7.

Table 12. IR frequencies of orphenadrine citrate functional group

Functional group	Assigned frequency [cm^{-1}]	Reported requency [cm^{-1}]
O-H stretching	3432.93	3550-3200
C=C stretching	1581.49	1650-1566
C-N stretching	1287.81	1342-1266
C-O (ester)	1177.61	1210-1163
C-H bending	1384.92	1385-1380

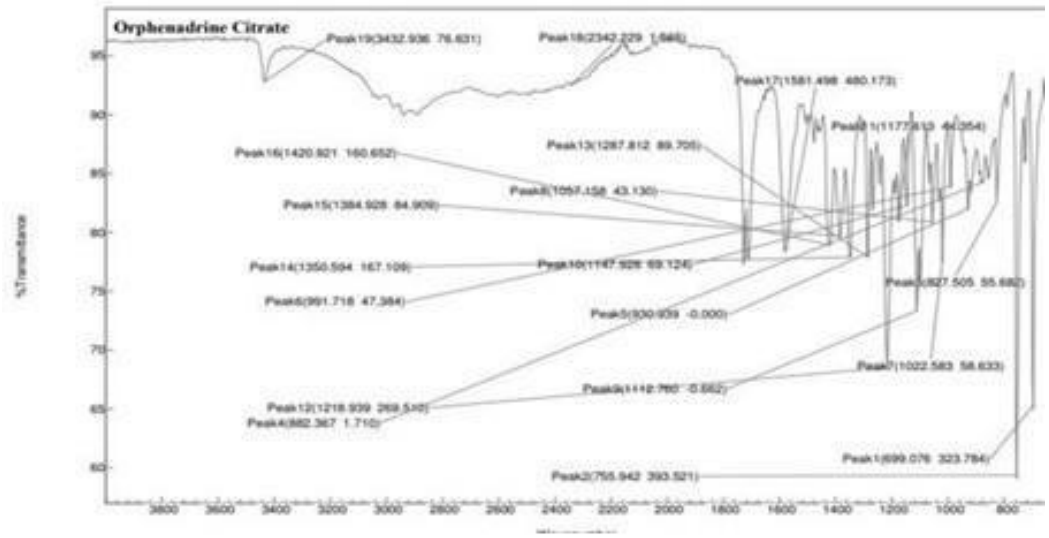

Figure 7. FTIR spectrum of orphenadrine citrate.

3.8. DRUG EXCIPIENT COMPATIBILITY STUDY

The FTIR spectra of paracetamol and orphenadrine citrate in pure form and their physical mixture was investigated and the result showed that there is no interaction between drug, polymer and excipients (Figures 8 – 11).

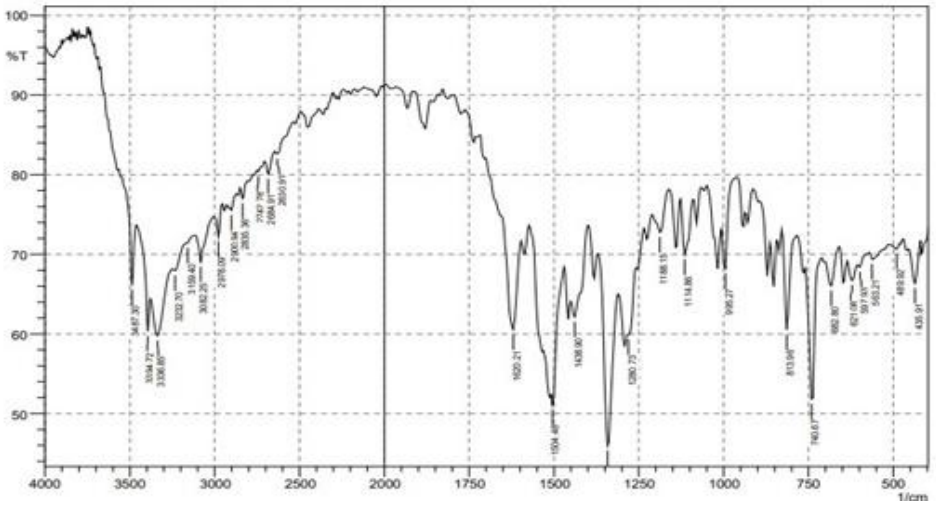

Figure 8. Compatibility IR for Paracetamol + Orphenadrine Citrate: Crosspovidone

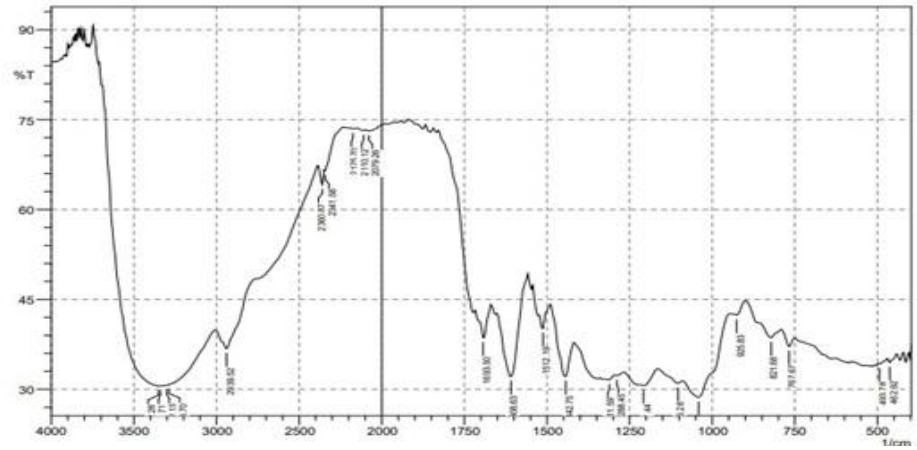

Figure 9. Compatibility IR for Paracetamol + Orphenadrine citrate: MCC

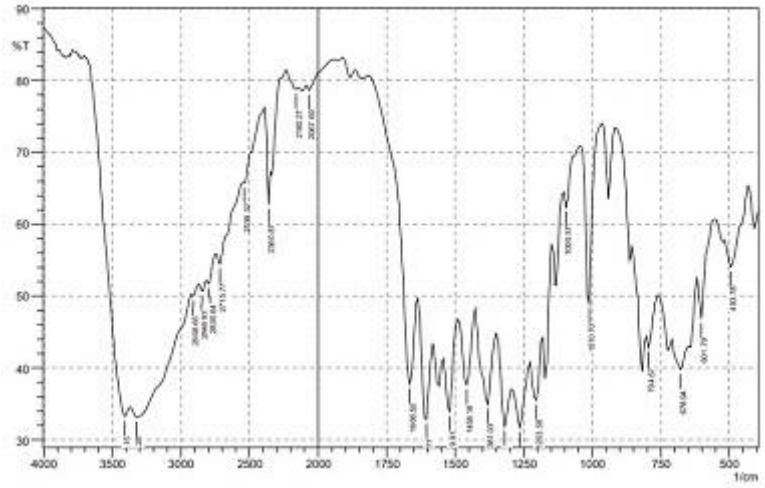

Figure 10. Compatibility IR for Paracetamol + Orphenadrine citrate : Mannitol

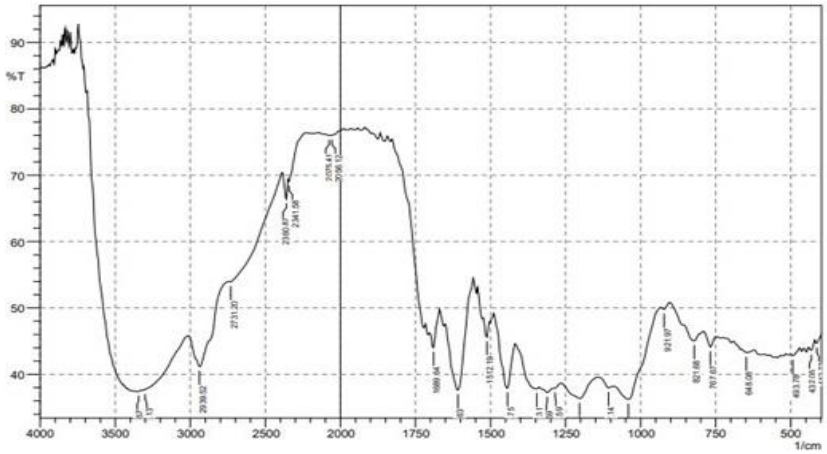

Figure 11. Compatibility IR for Paracetamol + Orphenadrine citrate : Magnesium stearate

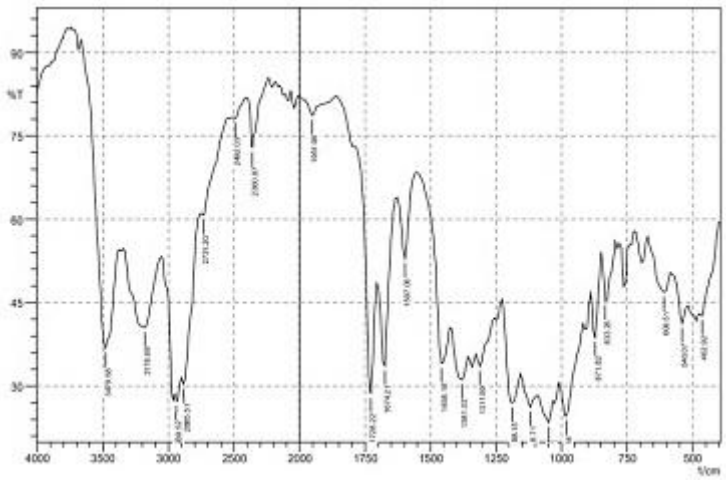

Figure 12. Compatibility IR for Paracetamol + Orphenadrine citrate :Talc

Table 13. Drug excipient compatibility

Ingredient	Ratio	Initial	Condition
			40°C/75% RH (Accelerated)
			1 month
Paracetamol	NA	White	NCC
Orphenadrine citrate	NA	White	NCC
Para + Orphenadrine:Cross povidone	1:1	Off white	NCC
Para + Orphenadrine:Microcrystalline cellulose	1:1	Off white	NCC
Para + Orphenadrine:Mannitol	1:1	Off white	NCC
Para + Orphenadrine:Magnesium stearate	1:1	Off white	NCC
Para + Orphenadrine:Talc	1:1	Off white	NCC

Note: NCC (no conformational change) in physical appearance from initial description, RH (Relative Humidity).

It can be seen from the above data that Paracetamol and Orphenadrine citrate combination was stable with all the excipients used for formulation and development.

3.9. FORMULATION OF IMMEDIATE RELEASE TABLET

Table 14. Formulation ingredients and its roles

S. No.	Ingredients	Role
1.	Paracetamol	Analgesic
2.	Orphenadrine citrate	Analgesic (Skeletal MR)
3.	Cross povidone	Super disintegrant
4.	Mannitol	Swelling agent, Diluent
5.	Microcrystalline cellulose	Binder
6.	Magnesium stearate	Lubricant
7.	Talc	Glidant

3.10. FORMULATION STRATEGY

Table 15. Formulation strategy

S. No.	Ingredients	Quantity [mg]								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1.	Paracetamol	450	450	450	450	450	450	450	450	450
2.	Orphenadrine Citrate	35	35	35	35	35	35	35	35	35
3.	Cross povidone	26	26	26	32.5	32.5	32.5	39	39	39
4.	MCC	32.5	48.7	65	32.5	48.7	65	32.5	48.7	65
5.	Mannitol	93.5	77.3	61	87	70.8	54.5	80.5	64.3	48
6.	Magnesium Stearate	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
7.	Talc	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Total weight of tablet		650								

3.11. EVALUATION OF FORMULATED BATCHES

3.11.1. Pre-compression parameters

The powder blend from all the batches were evaluated for density and flow property parameters which includes Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose. The results were expressed as follows in Table 16.

Table 16. Pre-compression parameters

Batches	Bulk density [g/cm^3]	Tapped density [g/cm^3]	Compressibility index [%]	Hausner's ratio	Angle of repose [degrees]
F1	0.535	0.635	15.75	1.19	26.20
F2	0.545	0.635	14.17	1.17	28.24
F3	0.524	0.609	13.96	1.16	26.98
F4	0.534	0.641	16.69	1.20	26.74
F5	0.522	0.632	17.41	1.21	25.34
F6	0.513	0.605	15.21	1.18	24.45
F7	0.543	0.645	15.81	1.19	27.36
F8	0.521	0.615	15.28	1.18	25.34
F9	0.531	0.625	15.04	1.18	25.15

3.11.2. Post compression parameters

Physical appearance. The tablets from all trial batches were white round shaped beveled edge with having plane upper and lower side.

Thickness and diameter. The thickness and diameter for all the tablets were measured by using Vernier caliper by picking the tablets randomLy. The values are almost uniform in all formulations. Thickness was found in the range from 3.25±0.20 mm to 3.43±0.21 mm respectively. Uniformity in the values indicates that formulations were compressed without sticking to the dies and punches.

***Hardness*.** Monsanto hardness tester was used for the determination of hardness for all the batches and results were expressed in table. Hardness was found to be in range of 3 kg/cm^2 to 5.5 kg/cm^2. The hardness for all formulated batches were uniform and possess good mechanical strength with sufficient hardness.

Friability. Tablets from all batches were evaluated by using Roche Friabilator and Friability of tablets was observed in acceptable range 0.42 to 0.73 (Less than 1%).

Table 17. Post compression parameters

Batches	Thickness [mm]	Diameter [mm]	Hardness [kg/cm^2]	Friability [%]
F1	4.27±0.01	12.79±0.01	3	0.56
F2	4.29±0.05	12.75±0.03	3.5	0.72
F3	4.32±0.05	12.76±0.02	4.5	0.52
F4	4.31±0.02	12.78±0.02	3	0.52
F5	4.31±0.01	12.78±0.02	4	0.47
F6	4.29±0.05	12.77±0.02	5	0.42
F7	4.32±0.05	12.75±0.02	3.5	0.67
F8	4.33±0.02	12.75±0.02	4	0.49
F9	4.29±0.01	12.76±0.02	5.5	0.73

Drug content uniformity test were performed for all formulated batches and results were expressed in Table 18. The drug content was found to be between 97- 103 % which was under specified limit. Among all the formulations F9 showed maximum drug release within 30 minutes.

Table 18. Drug content results

Batches	Drug content [%]	
	Paracetamol	Orphenadrine citrate
F1	98.93	100.41
F2	98.44	99.99
F3	99.12	102.65
F4	100.55	102.45
F5	99.03	100.50
F6	101.98	98.21
F7	100.88	99.84
F8	99.45	102.55
F9	101.38	101.28

***Weight variation*.** Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniforms weight due to uniform die fill. The tablets for all prepared batches were obtained in the range with acceptable weight variations as per pharmacopoeia specifications less than 5% (Table 19).

Table 19. Weight variation results

Batches	Weight variation	
	Weight [mg] ± S.D	Weight variation (5%)
F1	635 ± 6	Passes
F2	667 ± 5	Passes
F3	647 ± 7	Passes
F4	661 ± 9	Passes
F5	655 ± 4	Passes
F6	672 ± 5	Passes
F7	665 ± 8	Passes

Batches	Weight variation	
	Weight [mg] ± S.D	Weight variation (5%)
F8	639 ± 6	Passes
F9	640 ± 6	Passes

Disintegration test. Disintegration time was performed for all formulated batches and results were expressed in table. The disintegration time was found in the range of 1.15 - 2.30 min. Disintegration time was directly proportional to concentration of super disintegrating agent and inversely proportional with binder concentration (Table 20).

Table 20. Disintegration time results

Batches	Disintegration time [min]
F1	1.35 ± 0.02
F2	2.10 ± 0.05
F3	2.30 ± 0.04
F4	1.28 ± 0.02
F5	1.48 ± 0.02
F6	2.02 ± 0.04
F7	1.15 ± 0.05
F8	1.25 ± 0.04
F9	1.37 ± 0.05

***In vitro* dissolution test.** The *in vitro* evaluation of all the formulated batches were carried out for 30 minutes by using 0.1N hydrochloric acid as dissolution medium and % CDR of individual drug was determined by using its respective equation on line (Tables 21 and 22).

Table 21. *In vitro* dissolution for paracetamol

Batches / Time (min)	Cumulative Drug Release [%]								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	22.55	15.78	13.66	25.69	25.65	21.36	27.65	25.67	23.45
10	41.56	30.66	29.47	44.36	45.23	42.85	45.36	44.78	42.78
15	60.98	49.82	46.99	63.78	66.75	62.37	65.99	62.85	62.56
20	79.41	66.95	62.98	81.88	85.22	75.21	79.32	78.69	75.89
25	92.15	77.86	76.65	95.66	92.78	86.29	89.75	88.65	85.46
30	98.44	88.99	87.48	98.26	99.35	95.77	99.21	98.94	98.55

Table 22. *In vitro* dissolution for orphenadrine citrate

Batches / Time (min)	Cumulative Drug Release [%]								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	16.32	15.65	16.88	15.33	17.50	16.58	15.89	15.96	16.87
10	38.56	35.66	35.81	36.14	39.16	38.66	39.65	36.44	39.55
15	60.77	58.44	55.66	58.75	60.19	60.98	61.77	59.75	60.32
20	72.69	70.33	72.36	71.69	72.66	75.77	77.68	78.99	75.88
25	85.65	79.65	81.89	86.44	85.33	87.33	89.36	88.14	86.49
30	96.45	85.94	89.42	97.63	98.33	96.76	99.56	99.28	98.23

3.12. OPTIMIZATION OF IMMEDIATE RELEASE TABLET

To study the effect of independent variables on responses Design Expert 7.0 software was used. Experimental design layout developed for nine possible batches of paracetamol and

orphenadrine citrate immediate release tablet as shown in Table 23. Out of the various models such as Linear, 2FI (Two factor interaction) Quadratic and Cubic which fit well was suggested by software and was tested for analysis of variance (ANOVA). Regression polynomials were calculated for the individual dependent variables and then one factor and perturbation graphs were obtained for each individual dependent variable. Mathematical models were generated for each individual dependent variable or response (R) and expressed as equation 1-2. X1 and X2 are the main effects which represent the average result of changing one factor at a time from its low to high value and X1 X2 are interaction terms show how the response changes when two factors are simultaneously changed.

Table 23. Layout of the Actual Design of DOE

Runs	Factor1	Factor 2	Response 1	Response 2
	A: % Cross Povidone	B: MCC	Disintegration time [min]	Hardness [kg/cm^2]
1	4	7.5	2.10	3.5
2	4	10.0	2.30	4.5
3	6	5.0	1.15	3.5
4	5	5.0	1.28	3.0
5	5	7.5	1.48	4.0
6	6	10.0	1.37	5.5
7	4	5.0	1.35	3.0
8	6	7.5	1.25	4.0
9	5	10.0	2.02	5.0

3.13. RESULTS FOR THE DISINTEGRATION TIME OF DOE (DESIGN OF EXPERIMENTS)

After entering the data in Design-Expert software, fit summary applied to the data after which the "2FI (Two factor Interaction) vs Linear " was suggested by the software. (The higher the F-Value, the lower the Corresponding P- Value) The F Value it is calculated by dividing two mean squares (Table 24).

Table 24. Fit summary table for Disintegration time of DOE

Source	Sum of Squares	Degree of freedom (df)	Mean Square	F Value	p-value Prob > F	
Mean *vs* Total	22.7211	1	22.7211			
Linear *vs* Mean	1.2614	2	0.6307	17.9287	0.0029	
2FI *vs* Linear	0.1332	1	0.1332	8.5568	0.0328	Suggested
Quadratic *vs* 2FI	0.0021	2	0.0010	0.0415	0.9599	
Cubic *vs* Quadratic	0.0351	2	0.0175	0.4313	0.7327	Aliased
Residual	0.0407	1	0.0407			

Total	24.1936	9	2.6882			

4. CONCLUSIONS

The present study was under taken to formulate and evaluate immediate release tablet of paracetamol and orphenadrine citrate by using cross-povidone as a superdisintegrant. Paracetamol which is antipyretic and orphenadrine citrate is skeletal muscle relaxant.the immediate release tablet used for discomfort associated with acute painful musculoskeletal conditions. It works by helping to decrease the pain. The study involves pre-formulation of drug and excipients, formulation and evaluation. Nine batches were prepared by using different concentration. The optimized formulation was selected according to the result found from the evaluation parameter of each formulation. Estimation of drug was carried out spectrometrically by UV method. The drug paracetamol and orphenadrine citrate was taken and formulated with different concentration of cross-povidone, mannitol, micro-crystalline cellulose, magnesium stearate and talc. The tablets were prepared by direct compression method and then it is punched after subjecting the blend to pre-compression parameters like angle of repose (25.15°), bulk density (0.531g/cm^3), tapped density (0.625 g/cm^3), carr's index (15.04 %), hausner ratio (1.18). the result obtained were satisfactory. the post compression parameters like hardness (5.5 kg/cm^2), weight variation (640 ± 6%), friability (0.73%), drug content for paracetamol (101.38%) and orphenadrine citrate (101.28%), disintegration time (1.37 sec) and *in vitro* dissolution studies paracetamol (98.55% at 30 min),as well as orphenadrine citrate (98.23 % at 30 min). Among all these formulations f9 was selected as optimized formulation. the prepared in-vitro dissolution studies of prepared immediate release tablet were compared with that of marketed formulations. Hence it could be concluded that the superdisintegrant based on immediate release tablet of paracetamol and orphenadrine citrate would be providing quick onset of action on administration.

REFERENCES

[1] Chien, Y.W., *Novel Drug Delivery Systems*, 2nd Ed., Dekker, New York, pp. 96-139, 1992.

[2] Singh, B.N., Oral route Drug Delivery. In: Swarbrick, J., 3rd Ed. *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, New York, pp. 1242-1248, 2007.

[3] Chien, Y.W., *Inf. Health.,* **9**(7),1294, 1983.

[4] Ghosh, T. K., *J. Drugs and the Pharmaceutical Sciences*, **34**, 1, 2005.

[5] Allen, L.V., Popovich, N.G., Ansel, H.C., *Ansel's Pharmaceutical dosage forms & drug delivery systems*, 8th Ed., Lippincott Williams & Wilkins, Baltimore, 2007.

[6] Syed, A., Shaweta, S., *International Journal of Biopharmaceutical & Toxicological Research*, **1**(1), 24, 2011.

[7] Aulton, M.E., *Pharmaceutics. The Science of dosage form design*, 2nd Ed., Churchill Livingstone, Edinburg, 2002.

[8] Leon, L., Herbert, A., Liberman, J.L., *The theory and practice of Industrial Pharmacy*, 3rd Ed., Lea & Febiger, pp. 293-303, 2000.

[9] McGinity, J., Felton, L.A., *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd Ed., CRC Press, Boca Raton, pp. 385-417, 2001.

[10] Raymond, C.R., Paul, J.S., Marian, E.Q., *Handbook of pharmaceutical exicipients*, 6th Ed., Pharmaceutical Press, London, pp. 130-691, 1999.

[11] Mayank, B., Sumedha, B., Gopal, G., *Scholars Academic Journal of Pharmacy,* **2**(5)**,** 398, 2013.
[12] Nancy, S., *International Journal of Pharmaceutical Sciences and Research,* **10**(8), 3607, 2019.
[13] Hazarika, J.N.R., Deb, P., *International Journal of Current Pharmaceutical Research,* **9**(3), 118, 2017.
[14] Rishikesh, M.A.B., *International Research Journal of Pharmaceutical and Applied Sciences,* **2**(5), 88, 2012.
[15] Nisarg, P., *Journal of Pharmaceutical Science and Bioscientific Research,* **3**(2), 58, 2013.
[16] Bhatt, R., *Journal of Drug Delivery and Therapeutics,* **9**(2), 132, 2019.