"IDENTIFICATION AND OPTIMIZATION OF PARAMETERS AFFECTING AN ACTIVE DRUG COATING ON CORE TABLETS"

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MASTER OF PHARMACY

IN

PHARMACEUTICAL TECHNOLOGY &

BIOPHARMACEUTICS

BY

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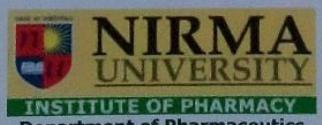

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CERTIFICATE

This is to certify that the dissertation work entitled "Identification and Optimization of Parameters Affecting an Active Drug Coating on Core Tablets" submitted by Ms. Khushali Modi with Regn. No. (013MPH108) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University and at Formulation Development Department, Piramal Pharmaceutical Development Services Pvt. Ltd., Ahmedabad under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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DECLARATION

I hereby declare that the dissertation entitled "Identification and Optimization of Parameters Affecting an Active Drug Coating on Core Tablets", is based on the original work carried out by me under the guidance Dr. Vinay Patil, Senior Principal Scientist, Formulation Development Department, Piramal Pharmaceutical Development Services Pvt. Ltd., Ahmedabad and Dr. Renuka Mishra, Assistant professor, Department of Pharmaceutics, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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To Whom It May Concern

This is to certify that **Ms. Khushali Modi** pursuing her M.Pharm from your esteem institute has successfully completed her project entitled "**Identification and Optimization of Parameters Affecting An Active Drug Coating on Core Tablets**" from 08th Sep 2014 to 08th May 2015 in our Formulation Department. We found her very dedicated & sincere about her work and we wish her all the best for her future endeavors.

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KHUSHALI MODI

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LIST OF ABBREVIATIONS

Sr. No	ABBREVIATIONS	FULL FORM
1	^{o}C	Degree centigrade
2	Abs	Absorbance
3	API	Active Pharmaceutical Ingredient
4	AV	Acceptance Value
5	Conc.	Concentration
6	CPE	Coating Process Efficiency
7	CU	Content Uniformity
8	DoE	Design of Experiment
9	FTIR	Fourier Transform Infrared Spectroscopy
10	g	Gram
11	HPMC	Hydroxypropylmethoxycellulose
12	IPQC	In process quality control
13	Kp	kilopond
14	m.Pa	millipascal
15	mg	Milligram
16	Min	Minute
17	PVP	Polyvinyl Pyrrolidone
18	q.s	Quatity sufficient
19	qty	Quantity
20	RSD	Relative Standard Deviation
21	USP NF	United States Pharmacopoeia National Formulary
22	USP	United States Pharmacopoeia
23	PhEur	European Pharmacopoeia
24	UV	Ultra violet
25	w/w	Weight by weight
26	WV	Weight variation
27	µ	Micron

Identification and Optimization of Parameters Affecting an Active Drug Coating on Core Tablets

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Active film coating is a process that enables uniform film formation on the surface of core tablets by spraying the coating liquid containing an Active Pharmaceutical Ingredient (API) dissolved or dispersed in coating material. The main objective of study was to identify the critical parameters that affect active coating on core tablets and to evaluate content uniformity of the API coated tablets. The target % RSD value was less than 6% and acceptance value was less than 15. Round and oval shaped tablets with two different weights 200 mg and 600 mg were taken and the influence of shape and weight on active coating was determined. Model drug was chosen as an API to be coated on the placebo core tablets and HPMC E5 was used as a film forming polymer. Pan load was optimized in the preliminary trials while spray rate and pan rpm was optimized using 3^2 full factorial design using Design Expert (9.0.4) software with % RSD and % CPE as dependent variables. The droplet size and droplet size distribution were analyzed using optical microscope to show the interaction and behavior of spray on core tablet surface. The results showed that round shape tablets were preferred over oval shape tablets. In particular round 200 mg tablets were the first choice of shape to be used for active film coating followed by oval 200, round 600 and oval 600 tablet. To ensure success in film coating process design (i.e. shape) of tablet along with formulation should be considered early in the development. Active drug coating also provides industrial application in tablet production of

low dose API as well as in preparing fixed dose combination tablets (immediate release API can be coated on the core tablets having modified release profile). It was suggested to use a side vented perforated coater to develop a coated tablet product containing an active agent in the film coat.

CHAPTER - 1

AIM OF INVESTIGATION

1. AIM OF INVESTIGATION

Solid oral dosage formulations are most favorable and widely used dosage form. Conventional drug delivery involves formulation of the API in the core tablet and then coating of core tablet to enhance the aesthetic appearance, to mask the bitter taste of drug or to modify the drug release.

In conventional process of tablet manufacturing, all the unit operations need to be tightly controlled and monitored to produce quality products. The tablet cores need to be coated eventually for the reasons mentioned above, so it would preferable to add the API in the coating solution itself and to spray on the inert tablet cores. With such an approach, only one unit operation involving API will be involved for monitoring quality of the product and therefore critical for the quality of the product.

For low dose API formulation, manufacturing with Direct Compression method may create issues related to compressibility as well as compatibility. Using wet granulation method, loss of API may occur at later steps. This issue can be resolved by using novel approach of active drug coating.

- The main **aim** of the present investigation is to identify the critical process parameters that affects the active coating on the core tablets and evaluate the content uniformity of the API coated tablets and achieve % RSD less than 6% and acceptance valueless than 15.
- To determine and analyze the effect of different tablet shape and weight on aqueous based active coating. To analyze the effect of different tablet shape on coating variability as these shapes could potentially be used to enhance a product's brand.
- To observe and troubleshoot various tablet defects occurring during optimization of the process parameters and predict the outcome of continuous coating operations.

CHAPTER - 2

INTRODUCTION

2 INTRODUCTION

2.1 INTRODUCTION TO TABLETS

Solid-dosage forms encompasses the largest category of dosage forms that are used clinically.

2.1.2 Definition: Tablets can be defined as the unit forms of solid medicaments prepared by compaction.

- Most common types of the tablets are those which needs to be swallowed as a whole and then disintegrates and releases the medicament in the gastrointestinal tract (GIT).
- Apart from this, other types of tablets are also designed to be chewed or placed under the tongue or along the buccal cavity.
- Moreover tablets with different release rates provide delayed or controlled release are referred to as complete drug-delivery systems.

2.1.3 Advantages of tablets [1, 2]

- Dose precision and least content variability
- Lowest cost compared to all other dosage forms
- Compact and light in weight, thus ease of handling
- Easy and cheap for packaging and shipping
- Product identification is simple
- Special release such as enteric or delayed release products can be easily formulated
- Highest chemical, mechanical and microbiologic stability among other dosage form.

2.1.4 Classification of Tablets [1]

Table 2.1: Types and classes of tablets

Oral Tablets for ingestion
Compressed tablets or standard compressed tablets
Multiple compress tablets
Layered Tablets
Compression coated tablets
Repeat action tablets
Delayed-action and enteric coated tablets
Sugar and chocolate coated tablets
Film coated tablets
Chewable tablets
Tablets used in oral cavity
Buccal tablets
Sublingual tablets
Troches and lozenges
Dental cones
Tablets administered by other routes
Implantation tablets
Vaginal tablets
Tablets used to prepare Solutions
Effervescent tablets
Dispersing tablets
Hypodermic tablets
Tablet trichurates

2.1.5. Evaluation parameters [1]

To monitor the production quality of tablets, quantitative evaluation of the physico-chemical and pharmacokinetic properties of the tablet becomes necessary. The parameters to be evaluated are as follows.

i. General appearance

Measurement of attributes such as tablets shape, size, color, odor, taste, surface texture, consistency and legibility of embossing debossing are involved.

ii. Size and shape

Consistent tablet thickness between batch to batch or within the batch can be achieved only if the particle size and size distribution of the granules or the powder blend is adequately consistent.

iii. Organoleptic properties

Quantitative evaluation of color can be done using Reflectance Spectrophotometer, Tristimulus Colorimetric measurements and the use of Microreflectance Photometer.

iv. Hardness

Defined as force required to break a tablet in a diameter compression strength. Various types of hardness tester namely Monsanto tester, Strong Cobb tester, Pfizer tester, Erweka tester and Schleuniger tester are used to determine the crushing strength of the tablet.

v. Friability

It is defined as tendency to crumble or it measures the effects of abrasion and shock. Roche Friabilator is used to determine the friability of the tablets.

vi. Disintegration time

Breakdown of the tablet into smaller particles or granules is known as disintegration time.

vii. Weight Variation

Weight variation test is the method of determining the drug content uniformity of tablets if the tablets were all or especially all (90 – 95 %) active ingredient or if the uniformity of the drug distribution in the granulation or powder from which the tablets are made.

2.2 INTRODUCTION TO TABLET COATING

2.2.1 Definition: Tablet coating is the application of coating composition to a moving bed of tablets with concurrent use of heated air to facilitate evaporation of solvent. [1]

2.2.2 Reasons for tablet coating [3]

- Substance which has property of bitter taste or unpleasant odor in the mouth is present in the core.
- Coating is added to improve stability if the substance is not stable in presence of light and is sensitive to moisture and atmospheric oxidation.
- The core is pharmaceutically non-elegant.
- Staining issues if the drug is colored and migrates easily.
- To reduce friction and increase the production rate.
- To modify release profile of drug, e.g. enteric coating, sustained release coating, osmotic pumps.
- To formulate a tablet dosage form with sustained release active pharmaceutical ingredient (API) in the core and the immediate release API in the coating layer.

2.2.3 Coating Process [1]

Most coating Process uses one of the three process.

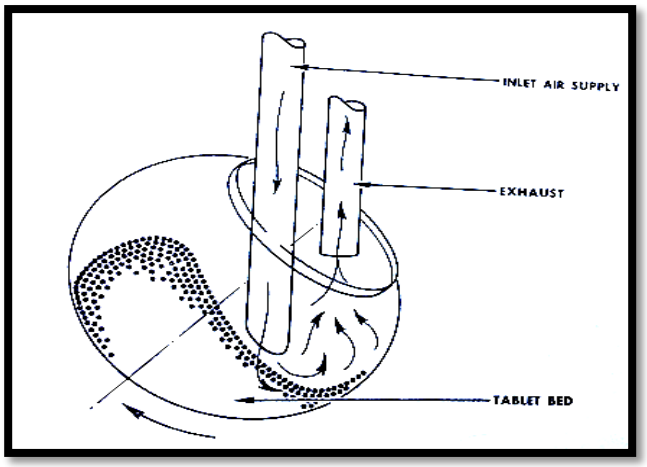
I. Conventional Coating Pan
II. Perforated Coating Pan
III. Fluidized Bed System (Air suspension)

I. Conventional Coating Pan

- The conventional coating pan system consists of a circular metal pan (0.8 to 6 inches in diameter) and rotates on its horizontal axis by a motor. Heated air is directed into the pan, tablet bed surface and is exhausted by means of ducts positioned through the front of the pan.

- Coating solutions are applied to the tablets by spraying the material onto the rotating tablet bed. Use of atomizing systems to spray the liquid coating material onto the tablets produces a faster more even distribution of the solution or suspension.
- Improvement in drying efficiency of the standard coating pan is obtained by the pellegrini pan, the immersion tube system and the immersion sword. The pelligrini system has a diffuser and baffled pan that distributes the drying air uniformly over the tablet bed surface.
- Newer models are completely enclosed which further increases drying and facilitates automated control. With immersion sword system, drying air is introduced through the perforated metal sword device that is immersed in the tablet bed. The drying air flows upward from the sword through the tablet bed. Since the air is intimately mixed with the wetted tablets a more efficient drying environment is provided.
- Coating solutions are applied by an atomized spray system directed to the surface of rotating tablet bed. A tube is immersed in the tablet bed with immersion tube system. The tube delivers the heated air and a spray nozzle is built in tip of the tube.
- The coating solution is applied simultaneously with the heated air system from the immersed tube. The drying air flows upwards through the tablet bed and is exhausted by a conventional duct. Relatively rapid processing times have been reported for both film and sugar coating with this system.

Figure 2.1: Diagram of conventional coating pan



II. Perforated Coating Pan

Equipment of this type consists of a perforated or partially perforated drum that is rotated on its horizontal axis in an enclosed housing. Perforated pan coater can be further divided into

i. **Accela Cota and Hi coater system:** Dry air enters into the drum and passes through the perforations in the drum.

ii. **Driacoater:** Dry air is introduced through the hollow perforated ribs located on inside of the drum. As the coating pan rotates, the ribs dip into the tablet bed and drying air directed up through and fluidizes the tablet bed. Exhaust occurs from back of the pan.

iii. **Glatt coater:** Dry air can be introduced from inside of the drum through the tablet bed and out of the exhaust duct. Drying air can also be directed by an optional split chambered plenum in the reverse manner up through the drum perforations for partial fluidization of the tablet bed.

Perforated pan systems are efficient drying systems with high coating capacity for sugar and film coating processes.

Figure 2.2: Diagram of Acela Cota

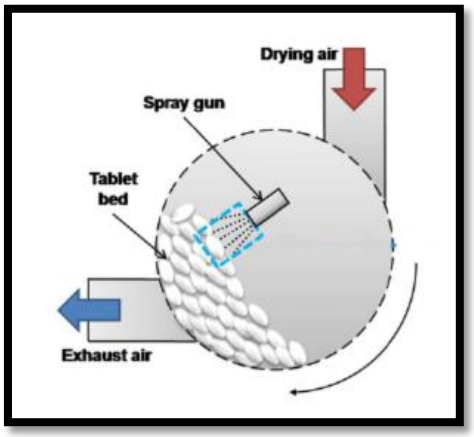


Figure 2.3: Diagram of Driacoater

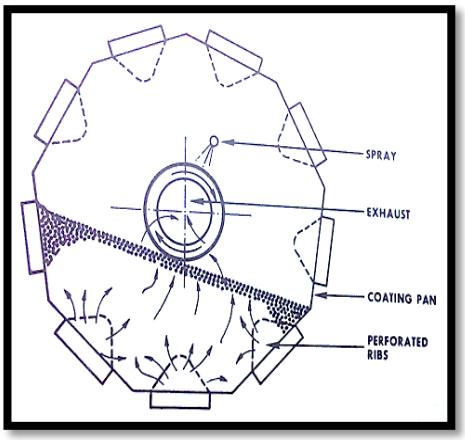
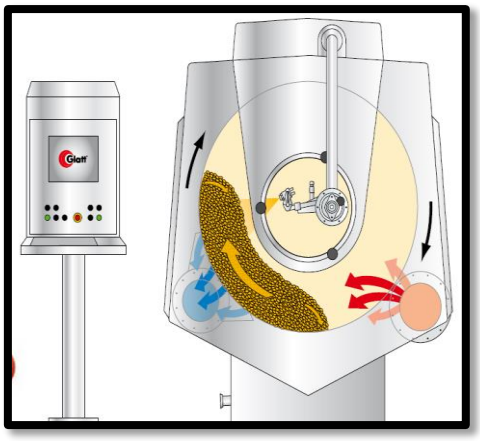


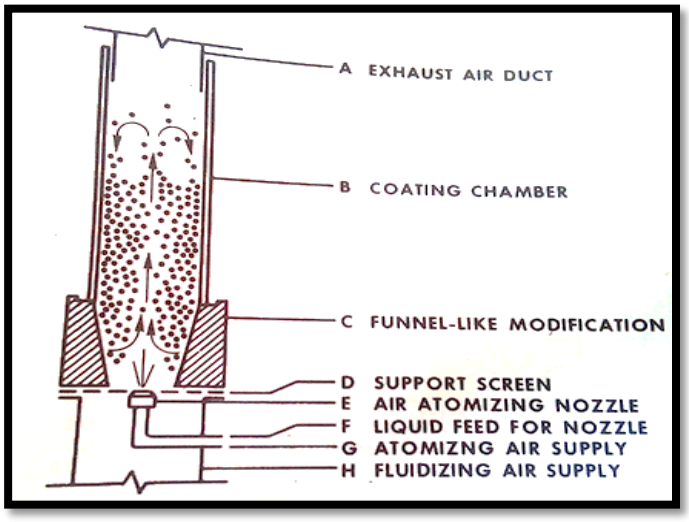
Figure 2.4: Diagram of Glatt Coater



III. Fluidized Bed Systems (Air suspension)

- The movement of tablets is upward through the center of the chamber. They fall toward the chamber wall and move downward to reenter air stream at bottom of the chamber.
- Coating solution are continuously applied from a spray nozzle located at the bottom of the chamber or are sprayed onto the top of the cascading tablet bed by nozzles located in the upper region of the chamber.
- **Limitation**: Tablet cores having high friability and prone to chipping and edge abrasion may be difficult to coat even under optimum conditions in bed systems resulting to relatively rough tablet to tablet impact and tablet chamber contact.

Figure 2.5: Diagram of a fluidized bed coater

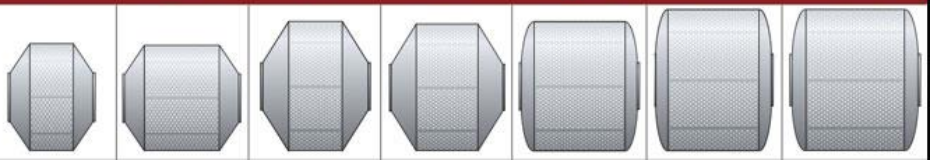


2.3 AQUEOUS BASED FILM COATING

- Aqueous film coating is employed to a large extent in pharmaceutical solid oral dosage form. Coating is practiced over 150 years for improving the aesthetic quality of dosage form, to mask the odor, taste, increasing the product stability, to modify the release rate of drug which ultimately lead to improved patient compliance. [4]
- A film coating is the application of thin polymer-based coat to a solid dosage form such as a tablet, granule or other particle.
- Close examination of the film structure reveals relatively non-homogeneous and quite distinct appearance that mainly results from the deliberate addition of insoluble ingredients such as pigments.
- This occurs because most coating processes rely on a single tablet or granule passing through a spray zone, after which the adherent material is dried before the next portion of coating is received. This activity is repeated several times until the coating is complete. The regulatory requirements are met if the % Relative Standard Deviation (RSD) is less than 6 % and acceptance value is less than or equal to 15.
- Number of problems need to be overcome for developing aqueous film coating. The main problem originates from low evaporation of water which can be solved by increasing the air flow rate or bed temperature.
- Heat transfer to aqueous phase is required for evaporation of water. There is an optimum air flow for each size of pan and results of several experiments have shown that bed temperature of 40-45^{o}C can be achieved if the inlet temperature is in the range of 50-80^{o}C.
- Tumbling of tablets is necessary for aqueous based coating. This means that tablets may suffer from erosion of surface and the edges. Optimizing the pan rpm can help to reduce the erosion. Moreover baffles prevent formation of slow motion of tablets at the center of the bed which might cause less coating as compared to rest of the batch. Baffles should be fully covered by the tablets to reduce the abrasion tendency. Moreover the pan should not be overloaded to reduce the efficiency of the baffles. [5]

- Aqueous film coating is a very crucial, multivariate and sensitive process wherein the quality of product is affected by number of variables. [4, 6]

Figure 2.6: Dimension for different capacity of pan

Technical Data	F48	F48XL	F60	F60XL	F60XC	F65C	F65XC
Drum Profile							
Drum Capacity	190 liters	270 liters	460 liters	530 liters	700 liters	820 liters	920 liters
Drum Diameter Inches, [mm]	48" [1220mm]	48" [1220mm]	60" [1525mm]	60" [1525mm]	60" [1525mm]	65" [1650mm]	65" [1650mm]
Typical Process Maximum	2500 CFM [4250 CMH]	3000 CFM [5100 CMH]	4000 CFM [6800 CMH]	4000 CFM [6800 CMH]	5000 CFM [8500 CMH]	5000 CFM [8500 CMH]	5000 CFM [8500 CMH]
Machine Dimensions	Width 81" [2058 mm] x Depth 102" [2591 mm] x Height 91" [2311 mm]						
Door Clearances	Front 72" [1830 mm], Sides 33" [838 mm], Rear 39" [990 mm]						

- The successful execution of coating is determined by mainly 3 factors

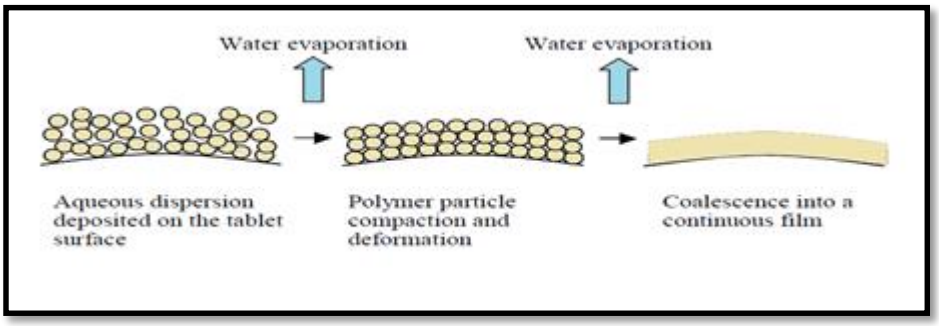
1. Core tablets formulation
2. Formulation of coating system
3. Process parameters affecting coating [7]

2.3.1 Film Formation Mechanism

- Aqueous film coatings are applied mainly as solutions or dispersions depending upon solubility of film forming polymers in water. Film formation is complex process which is dependent on coating polymer, polymer molecular weight, particle size, coating solutions viscosity and surface tension, coating and storage conditions.
- Cohesive force forms a bond between the molecules of coating polymer when the coating polymer is applied on the tablet surface. [8]
- Diffusion is responsible for coalescence of adjacent polymer molecular layers. The cohesive strength of polymer must be relatively high to obtain high cohesion.

- The viscosity of the solution increases when most of the water evaporates and leaves behind a close proximity of polymer chain which gets deposited over previous layers of polymer. If sufficient cohesive attraction occurs between the molecules and if coalescence causes complete evaporation of residual water, individual polymer chain aligns themselves to form a cohesive film. [9]

Figure 2.7 Film formation from aqueous polymer dispersion



- Evaporation of water is mainly responsible for coalescence of aqueous polymer dispersion deposited on surface of tablet in the form of a continuous film. Dispersed Polymer particles gradually fills up the void spaces and forms a closely packed ordered array and fuse together to form a film.
- Coalescence takes place when the adhesion forces are greater than the resistive forces of nearby particles. The forces which plays a major role here are the water-air interfacial tension (capillary pressure) as well as the water particle and air particle interfacial tension. Homogenous film formation occurs as a result of autohension (inter-diffusion of polymer chain) occurring through the interface of the particles. [10, 11, 12]

2.3.2 Components for Film Coating Formulation [13, 14]

Film-coat formulations mostly contain the following components:

- Active Pharmaceutical Ingredient (API)
- Polymer/Film Former
- Plasticizer
- Pigment/opacifiers

- Vehicle.
  - Plasticizers by no means are used universally though they have an established place in film-coating formula.
  - Nowadays with advent in the pharmaceutical advancement consideration is also given to minor components in a film-coating formula such as flavors, surfactants and waxes and, in rare instances, the film coat itself may contain active material. [3]

API:

Generally the API which undergoes acid or base catalyzed hydrolysis can be used for active film coating approach. This will solve the issue of chemical stability. Moreover API to be given in combination with other drug with different release profile can be incorporated in coating layer with other drug in the core. [15]

Film Formers:

Pharmaceutical film formers are flexible linear macromolecules having molecular weight ranging between 10,000 and several million Daltons. Ideal properties for polymers used in film coating are

a) Solubility in a wide range of solvent in order to allow flexibility in coating formulations
b) Ability to produce films with adequate mechanical properties
c) Stability against light, oxygen, hydrolysis
d) Low toxicity
e) Optimum dissolution in gastrointestinal tract

- During the coating process there are several polymer characteristics that are important such as solubility, solution viscosity, film permeability and mechanical properties (strain, tensile strength, elastic modulus).
- Majorly either cellulose derivatives, the cellulose ethers, or acrylic polymers and copolymers are used for film coating. Occasionally high molecular weight Polyethylene Glycols (PEG), Polyvinyl Pyrrolidone (PVP), Polyvinyl Alcohol (PVA) and waxy materials are also used for the film coating purpose.

Table 2.2: Examples of common polymers used in film coating

Polymer class	Examples
Cellulosic	Hydroxypropylcellulose Hydroxypropylmethylcellulose Hydroxyethylcellulose
Vinyl	Poly (vinyl pyrrolidone) Poly (vinyl alcohol) Poly (vinyl pyrrolidone), poly (vinyl acetate) copolymers Poly (vinyl alcohol), poly (ethylene glycol) copolymers
Glycols	Poly(ethylene glycols)
Acrylics	Amino alkyl methactylate copolymers
Other carbohydrates	Poly (vinyl pyrrolidone) Poly (vinyl alcohol) Poly (vinyl pyrrolidone), poly (vinyl acetate) copolymers Poly (vinyl alcohol), poly (ethylene glycol) copolymers

- Polymer is dissolved in an appropriate solvent usually water or a non-aqueous solvent to form a film coat on the solid dosage form. However, some of the water-insoluble polymers are available in a form which renders them usable from aqueous systems. These materials find considerable application in the area of modified release coatings. [15]

Plasticizers: [16]

Plasticizers are not required when tablets possess sufficient hardness and low friability are used and little or no pigment is contained in the coating formulation [16]. Plasticizers are intended to modify the glass transition

temperature and helps to control the behavior of the films. Water acts as a plasticizer in presence of HPMC and causes reduction of glass transition temperature of the system. Transition from glassy to rubbery state occurs due to formation of polymer chain. Due to imbibition of water, HPMC swells and results in changes of polymer and drug concentration and increases dimensions of the systems. [17]

The key points to be considered during selection of the plasticizer in coating solution is

- Efficiency: defines amount of plasticizer to be added to produce the desired effect.
- Compatibility: indicates how effectively the interaction of plasticizer with polymer occurs and the level to which that interaction occurs.
- Permanence: relates to both plasticizer–polymer compatibility and plasticizer volatility.

Table 2.3: Common plasticizer used in film coating formulation

Class	Example
Polyhydric alcohols	Propylene glycol
	Glycerol
	Polyethylene glycols
Acetate esters	Glyceryl triacetate (Triacetin)
	Triethyl citrate
	Acetyl triethyl citrate
Phthalate esters	Diethyl Phthalate
Glycerides	Acetylated monoglycerides
Oils	Castor oil
	Mineral oil

Colorants and Opacifiers:

Colorants are added during film coating formulations for following reasons

- Helps in product identification
- Improve product appearance
- Improve product stability

These are aluminum lakes, iron oxides or natural colors such as Riboflavin and Carotenoids. Certain opacifiers like Titanium dioxide or materials with high refractive indices can be introduced to protect light-labile drugs and avoid translucent films. The use of pigments and opacifiers may be omitted from the formulation if a clear coating is required. [16]

Table 2.4: **Common types of colorant used in film coating formulation**

Type	Examples
Water soluble dyes	FD&C yellow #5 FD&C blue #2
Natural colorants	Riboflavin Beta-carotene Carmine lake
FD&C lakes	FD&C yellow #5 lake FD&C blue #2 lake
D&C lakes	D&C yellow #10 lake D&C red #30 lake
Inorganic pigments	Titanium dioxide Iron oxides

Solvent/Vehicle:

- Water is the most preferred solvent used in modern film coating.

  Water is used as a solvent for following reasons:

  - Has high latent heat of vaporization property, requiring more energy input to the coating process to ensure that effective drying takes
  - Aqueous coating systems have higher surface tensions than organic solvent based, thus impacts wetting and adhesion on various types of pharmaceutical tablets (e.g., vitamins).

- Due to high viscosity, aqueous coating systems have some impact on pumping and atomization efficiency than organic solvent-based systems. [16]

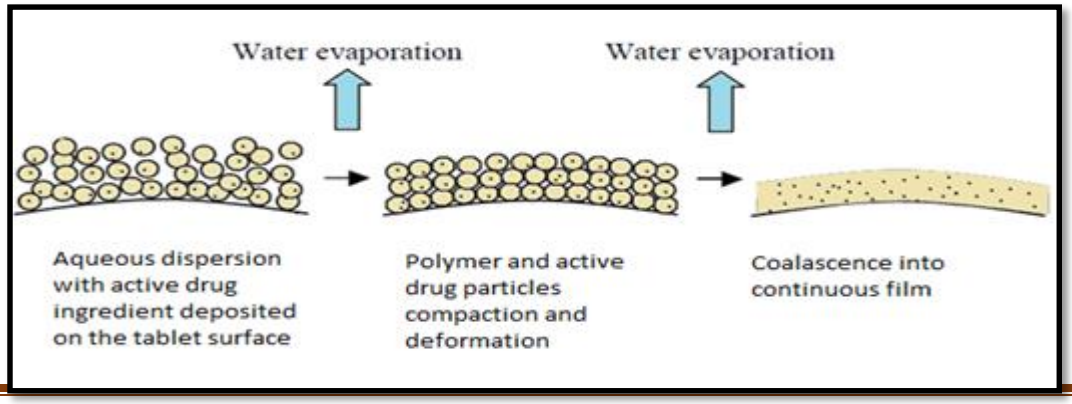
Table 2.5: List of common solvents used in film coating

Class	Examples
Aqueous	Water
Alcohols	Methanol Ethanol Isopropanol
Esters	Ethyl acetate Ethyl lactate
Ketones	Acetone
Chlorinated hydrocarbon	Methylene Chloride 1:1:1 Trichloroethane Chloroform Dichloromethane

2.4 ACTIVE FILM COATING

- **Active film coating** is a process that enables uniform film formation on the surface of core tablets by spraying the coating liquid containing an active pharmaceutical ingredient dissolved or dispersed in coating material. [15]
- For the majority of tablet formulations, drugs are in core of tablets. Unit operations such as mixing of drug and excipients, dry or wet granulation, milling, lubrication and tablet compression are involved in the manufacturing of tablet. All these unit operations need to be tightly controlled and monitored to produce quality products.
- The tablet cores need to be coated eventually for the above mentioned reasons, it would make sense to add the drug in the coating solution itself and to spray on the inert tablet cores. Here, only one unit operation involves drug substance and critical for quality of the product.
- In an active coating process, the uniformity of coating is a critical quality attribute as coated tablets have to pass the test of uniformity of dosage units according to various pharmacopoeias. [18]
- The regulatory requirements are met if the acceptance value is less than or equal to 15.
- Hence to comply with this pharmacopoeial requirements process understanding is required thoroughly. Moreover, the coefficient of variation of the API content in the tablet coat must not exceed 6 % provided that the correct coating endpoint is met.

Figure 2.8: Mechanism for aqueous active film formation



2.4 .1 Challenges of the approach [15]

Three main challenges of the approach are as follows:

i. To determine the coating end-point.

- Weighing the tablet samples periodically throughout the coating operation, end point of the active coating process may be determined to get the average tablet weight gain and when the tablets have gained the target weight, the coating process is stopped.
- In-process Assay can be performed at different time intervals to determine the actual quantity of the API and coating material deposited on the tablet. This analysis can help to know whether spraying of additional suspension or solution of the coating suspension is needed or not.
- Actual amount of API deposited on core tablets and the coating time shows linear relationship if spray rate is kept constant while performing the coating.

ii. To achieve consistent tablet coating uniformity.

- The coating uniformity can be achieved by evaluating the physical parameters of the tablet and coating process parameters. This will help to indicate the relative standard deviation of the API on the core tablets.

iii. To maximize the amount of active deposited during the coating process.

- Here, volume of drug coating solution or suspension prepared for the active process must contain some excess amount, to cover the material loss during spraying.
- Moreover, coating process cannot be expected to be 100% efficient as there will be some loss of coating suspension/solution.
- Production loss of drug due to limited active coating process efficiency is of concern due to high cost of drug.
- The cycle time can be reduced if the efficiency of the coating process is improved.

2.4.2 Application of the approach [15]

- To improve the **chemical stability of a drug molecule** by incorporating drug in coating layer of film coated tablets for the drugs which are likely to undergo acid or alkali degradation.
- It acts as an effective **strategy to minimize the chemical interaction** between different drug molecules by physically separating one active compound from core tablet containing active agent by developing fixed dose combination for tablets.
    - E.g. Modified release dose in tablet core and an immediate release dose in the coating layer can be done for a fixed dose combination of drug.

2.5 INTRODUCTION TO FACTORS AFFECTING COATING [13, 19]

Parameters affecting coating

i. Spray dynamics

ii. Uniformity of spray application

iii. Uniformity of product movement

iv. Evaporative capacity

i. Spray Dynamics:

Selection of spray rate is dependent on spray gun's ability to produce a consistent droplet size distribution. Increase in spray rate leads to increase in the droplet size distribution. Factors to be taken into consideration while determining the spray rate are

- **Solution viscosity:** With increase in solution viscosity the the acceptable droplet size distribution will decrease.
- **Spray pattern width:** The ideal gun to gun spacing is 12-20 cm. At spacing greater than 20 cm, the uniformity of the spray across the pattern starts to deteriorate. Wider the spray pattern width, greater will be the spray rate per gun.
- **Product movement:** The movement of product is mainly affected by the baffle design, pan speed, tablet size and shape.

ii. Uniformity of Spray Application

- **Spray Gun Design**:
  - Mostly air atomizing or pneumatic type of gun is used. This gun allows for variable spray rates. In the past hydraulic guns were used for due to limitation of flexibility in spray rates there use has declined.
- **Number of Spray Guns**:
  - Adequate number of spray gun should be used to provide uniform coverage from front edge to back edge of the entire tablet bed in the pan. Additional guns should be used only if the current number of guns are insufficient to cover the area of tablet bed.

- Spray guns are able to develop pattern widths of 12-20 cm, but for pattern width greater than lead to recombination of droplets which ultimately leads to distortion of droplet size distribution. The chances of over-wetting increases due to overlapping of spray patterns.

- **Uniform gun – to – gun Solution Delivery:**
- The current trend in the coating system is the use of single pump for multiple spray guns and hence it becomes necessary to calibrate the spray gun regularly to ensure the same quantity of the solution is delivered each time.
- Moreover calibration using only water is not satisfactory as the viscosity of water is less compared to the viscosity of coating solution.

- **Atomization Air Volume/Droplet size:**
- Atomization air volume can be adjusted to obtain desired mean droplet size of the spray. Increase in the atomization volume, causes decrease in mean droplet size.
- Moreover increase in spray rate or solution viscosity causes increase in the mean droplet size. So, the evaluation of the droplet size should be done at the exact spray rate at which coating has to be done.

- **Spray Gun Angle:**
- Spray gun is placed between the leading and trailing edges of the tablet bed, at 90^o angle to the moving tablet bed. If the spray guns are not directed at 90^o angle to the tablet bed, then the spray has the tendency to build up on the wings of the air cap as it exits the solution nozzle.

iii. Uniformity of Product Movement

- **Pan Speed**
- The minimum pan speed and uniformity of product movement is necessary to achieve uniform application of coating solution. Once the pan speed has been determined, scale up can be done by duplicating the peripheral edge speed, by taking the ratio of the small pan to large pan diameter times the small pan speed.

- The pan speed has impact on the time the tablets spend in the spraying zone and subsequently the homogeneous distribution of the coating solution on the surface of each tablet throughout the batch.
- Increasing the pan speed improves the uniformity of coating and decreases the coating thickness variation.
- Too high pan speed causes the tablet to undergo excessive attrition and breakage, while low pan speed causes sticking or twinning.

- **Tablet size/shape**
  - Flow characteristics will differentiate depending upon the size and shape of the tablet. Smaller tablets flow better than the bigger tablets. Longer and less round shape will tend to slide and flow more poorly than other shapes.
  - Product flow must be reexamined if the tablet shape and size are changed. If the size of the tablet is too small than fine mesh is required to cover up the perforations in the pan to prevent the exhaust of product.

- **Baffle size/type and number**
  - Variety of different baffle sizes and shapes are available. Main function of the mixing baffle is to transfer the product between the front and back of the coating pan. Standard size baffles used with a small batch will result in sluggish movement of the product.
  - During the pan rotation baffles will temporarily carry a portion of tablets out of the tablet bed, causing a small increase in gun to bed distance. As these tablets cascade off the baffle, the tablet bed height rises and the gun to bed distance decreases. Variation of 2.5-5.0 cm is typically observed during the coating process.
  - A minimum variation in the gun to bed distance is desired so that spray droplets striking the tablets have a constant moisture level.

- **Batch Size**

- Acceptable batch size ranges from 50-80% of the pan volume. For smaller batches around 50% in a perforated coating pan, unless the process air is blocked off, the process will preferentially pass around the tablet bed, due to less restriction or pressure drop.
- The coating can however be carried out but it leads to decrease in the drying efficiency. Using 95% of the batch size instead of 100% can eliminate spillage out of pan mouth.

iv. Evaporative Capacity

- **Process air volume**

- The inlet air volume is more important than the exhaust air volume as an indicator of the evaporative capacity since this air passes through the tablet bed and vaporizes the water from the tablets.
- The exhaust air temperature may be slightly higher than the inlet air temperature due to addition of the nozzle air from the spray guns and also due to the leakage that may exist. Large difference in the inlet and exhaust air temperature due to leakage may be a problem as air can artificially depress the exhaust temperature.

- **Spray rate**

- Spray rate can be chosen based on practical approach depending upon tablet size and shape. Spray rate can be determined by the evaluating the quality of droplet size distribution.
- Spray rate for aqueous film coating vary from 6-30g/min for small 2.0L pan, to 80-250g/min/gun in a large production scale pan. Viscosity of coating solution, type of spray gun and the film quality desired are the key factors that limit maximum spray rate per gun.

- **Spray gun to tablet - bed distance**

- For small scale coating systems, the gun-to-bed distance can be as little as 2.5 to 5.0 cm. For a production sized coating pan the typical gun to bed distance is from 20 to 25

cm. This distance usually provides an idea of the number of guns needed to adequately cover the spray zone and the desired quality of spray.

- If the gun-to-bed distance is less than 20 cm, then either the inlet temperature and product temperature are increased or the spray rate must be reduced, to compensate for the shortened evaporation time. If this distance is greater than 20 cm, the inlet process temperature should be reduced otherwise more spray drying will occur.

- **Exhaust Temperature**
- The standard approach to the film-coating process utilizes an exhaust temperature of 38^{o}C to 44^{o}C. Based on the desired spray rate, an inlet temperature is determined that allows the target exhaust temperature to be maintained.
- Greater is the distance between the exhaust and product temperature probes, the greater the differential.
- The product temperature can be determined by using either a probe that extends into the tablet bed or through the use of an infrared temperature probe directed just above the spray zone.

- **Dew Point Temperature:**
- Is a direct measure of moisture contained in the air and is measured by either a capacitance or a chilled mirror type dew point sensor. High dew point can be controlled through use of dehumidification either via chilled water coils or a dessicant dehumidification.
- Chilled water systems are usually specified to control the dew point at 10^{o} to 12^{o}C.
- If no attempt is made to limit the variation of the inlet dew point then fluctuations in ambient air conditions can lead to reduced coating efficiency, longer processing times or film defects due to over-wetting.

- **Consideration of Product substrate:**

To develop the effective tablet coating process product must be evaluated to ensure the necessary criteria for a substrate are achieved.

- **Hardness**

- The tablet cores must be capable of withstanding the tumbling rigors during rolling inside the coating pans. Tablet hardness tester is used to determine the edge to edge tablet hardness. Hardness can be measured in Strong Cobb (Sc), kilopond (kp), and Newton (N).

Table 2.6: Desirable hardness depending on tablet size

Tablet size	Desired Hardness
Small tablets (100mg)	2-6 Kp
Medium size	12-16Kp
Large Capsule size(≥ 1g)	>20 Kp

1 Kp = 9.807 N or 1.4 Sc

- Tablet hardness has traditionally been the measure of tablets sustainability for coating. In many cases the tablet may be of adequate hardness but may still pose problem of capping or show excessive wear on the tablet edges or logo. Thus slightly better means of determining the tablets ability to withstand the tumbling is friability.

- **Friability**

- Friability is usually determined by tumbling a certain number or weight of tablets for a set number of rotations inside a cylinder which is usually 100 revolutions.
- The weight loss is calculated before and after tumbling and expressed as percent friability. New innovation to the friability is keeping the mesh screen inside the friability cylinder.
- This can provide a better correlation between the friability test and actual coating sustainability. In general friability of less than 0.1% or lower should be sufficient to avoid attrition problems during coating process.

- **Weight Variation**

- Wide tablet weight variation makes it difficult to determine the actual tablet weight gain due to application of film coating since the weight variation in the uncoated cores can be greater than the weight of the film to be applied.
- Moreover wide variations in the tablet weight can lead to variation in the hardness of the tablet.

- **Stability**

- The product must be able to withstand the temperature and humidity conditions and remain stable during the coating process. Due to evaporative cooling, product air temperature is significantly less than that of inlet air during the coating process. Tablets should be able to handle the usual product temperature of 35 to 50^{o} C.

- **Shape**

- Tablets with sharp edges may have greater tendency for edge wear and tear so should be avoided for film coating like the. Poor product movement and twinning may result with tablets having large flat surfaces. Adding slight concavity may help to decrease the agglomerative tendency.

- **Logo Design**

- Sharp corners or small islands on the tablet logo can lead to logo attrition problems. If the logo is too fine or contains too much detail, the film-coating may bridge or cover the logo. A draft angle of 35^{o} is recommended for film-coated tablets.

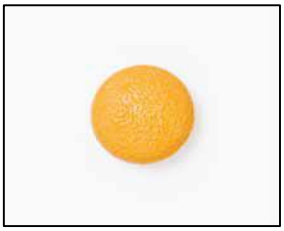
- **Core Porosity**

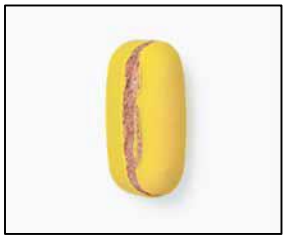
- Good adhesion must exist between the tablet surface and film coating. Poor porosity of the core tablet might result in low adhesion which will ultimately lead to picking or peeling of the film. This can be overcome by use of more adhesive film polymers (like Hydroxypropylmethylcellulose, Hydroxyethylcellulose).

2.6 DEFECTS IN TABLET COATING [20, 21, 22]

Variation in the formulation and processing conditions may result in unacceptable quality defects in the film coating. The source of these defects and some of their probable causes are describe in table no 2.7

Table 2.7: Types of defects in tablet coating

Problem	Description	Possible reason	Remedy
Orange Peel /Roughness 	Rough or uneven surface f the tablets	- Distance between nozzle and tablet bed is incorrect - Spray angle is wrong - Spray drying - Sedimentation of the dispersion - Viscosity/solid content is too high - high friability	- Increasing the spray rate - Decreasing the drying capacity - Reducing the atomizing air pressure - Decreasing the viscosity - Optimizing the distance between nozzle and tablet bed
Logo Bridging 	Filling of the logo or the break line	- Viscosity is too high - Plasticizer content is too low - Spray rate is too high - Atomizing air pressure is not proper i.e (too low or too high)	- Decreasing the viscosity -Increasing the plasticizer content - Reducing the spray rate - Adjusting the spray pressure(increase or decrease)
Twinning 	Two or more tablets stick together	- Over humidification - Process air volume is too low - "Planar" shape is not suitable	- Reducing spray rate - Increasing the drying capacity - Using release agents in the formulation
Sticking and ripping off Coating 	Tablets rip off the coating from each other	- Pan speed is too low - Air temperature is too low - Process air volume is too low - Spray rate is too high - Process is too damp	- Increasing the pan speed - Increasing the inlet air temperature - Increasing the process air volume - Reducing the spray rate

Scuffing 	Formation of Gray layer forms on tablet surface	-Titanium dioxide quantity is too high - Interaction between drum wall and coating	- Reducing the titanium dioxide - Spraying the drum prior to the trial
Capping 	Detachment of the film surface	- Hygroscopic core - Disintegrants are used	- Using a subcoat -Optimizing process parameters
Colour variation 	Batch has heterogeneous colour or Individual tablets have heterogeneous color	- Coverage properties of the coating are insufficient - Solid content of the suspension is too high - Weight gain level is too low	- Increasing the coverage properties of the coating (more pigments) - Reducing the solid content - Increasing the weight gain level
Peeling 	Spalling of the film – possible cracking of the coating	- Tablet is swelling - Plasticizer content in coating suspension is too low - Tablet is too wet - Tablet hardness is too low - Tablet is outgassing	- Increasing the plasticizer content - Increasing the film forming polymer

2.7 UNIFORMITY OF DOSAGE UNIT [23]

- Dosage units are defined as dosage forms containing a single dose or a part of a dose in each unit.
- To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim.
- The term uniformity of dosage unit is defined as the degree of uniformity in the amount of the drug substance among dosage units.
- The uniformity of dosage units can be demonstrated by either of two methods, Content Uniformity or Weight Variation. The test for Content Uniformity is based on the assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual content is within the limits set. The content Uniformity method may be applied in all cases.

Table 2.8: Weight variation test for following dosage forms

W1	Solutions enclosed in unit-dose containers and into soft` Capsules
W2	Solids (including powders, granules, and sterile solids) that are packaged in single-unit containers and contain no active or inactive added substances;
W3	Solids (including sterile solids) that are packaged in single- unit containers, with or without active or inactive added substances, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation
W4	Hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting the requirements for *Content Uniformity*

Table 2.9: Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	**Type**	**Subtype**	**Dose and Ratio of Drug substance**	
			≥ 25 mg and ≥25%	**<25 mg and <25%**
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single unit container	Single component		WV	WV
	Multiple components	Solution Freeze dried in final container	WV	WV
		Others	CU	CU
Solutions in unit dosage containers and into soft capsules			WV	WV
Others			CU	CU

2.7.1 Content Uniformity [23]

Not fewer than 30 units are selected and process as follows for the dosage form designated. Where different procedures are used for assay of the preparation and for the content uniformity test, it may be necessary to establish a correction factor to be applied to the results. Solid dosage forms: Assay 10 units individually using an appropriate analytical method.

Table 2.10: Calculation of acceptance value

Variable	Definition	Condition	Value
$\bar{x}$	Mean of individual contents ($\chi 1, \chi 2, \ldots, \chi n$), expressed as a percentage of the label claim		
$\chi 1, \chi 2, \ldots, \chi n$	Individual contents of the units tested, expressed as a percentage of the label claim		
n	Sample size (number of units in a sample)		
k	Acceptability constant	If n = 10, then k=	2.4
		If n = 30, then k =	2.0
s	Sample standard deviation		
RSD	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		100s/ $\bar{x}$
M (case 1) to be applied when T $\leq$ 101.5	Reference value	If 98.5% $\leq \bar{x} \leq$ 101.5%, then	M = $\bar{x}$ (AV = ks)
		If $\bar{x}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\bar{x}$ + ks)
		If $\bar{x}$>101.5%, then	M = 101.5% (AV = $\bar{x}$ – 101.5 + ks)

M (case 2) to be applied when T>101.5	Reference value	If $98.5 \leq \underline{\bar{x}} \leq T$, then	M = $\bar{x}$ (AV = ks)
		If $\bar{x}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\bar{x}$ + ks)
		If $\bar{x}$>T, then	M = T% (AV = $\bar{x}$ – T + ks)
Acceptance value (AV)			general formula: $/M - \bar{x}/+$ ks (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance value		L1 = 15.0 unless otherwise specified
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	On the low side, no dosage unit result can be less than [1 (0.01)(L2)]M, while on the high side no dosage unit result can be greater than [1 + (0.01)(L2)]M. (This is based on L2 value of 25.0.)	L2 = 25.0 unless otherwise specified
T	Target content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. Unless otherwise stated, T is 100.0 per cent, or T is the manufacturer's approved target content per dosage unit.		

2.7.2 Coating uniformity [18]

The coating uniformity (CU) can be differentiated into two types

1. The intra-tablet CU – represents homogeneity of film on a single tablet and can be characterized for instance by Terahertz Pulsed Imaging (TPI) which enables the measurement of coating thickness distributions or by Optical Coherence Tomography (OCT).
2. The inter-tablet coating uniformity – refers to the homogeneity between the different tablets within one batch. It can be determined by TPI, mass uniformity or content Uniformity. Computational simulation tools like the Discrete Element Method (DEM).

2.7.3 Coating process efficiency [24]

- The coating process efficiency (CPE) is the actual amount of coating applied to the tablets relative to the theoretical amount applied [25]. It is a good measure to indicate over wetting or over drying. In case of over wetting, coating solution or suspension can be transferred from the tablets to the wall of the coating pan, which reduces the CPE.
- On the other hand, in case of over drying the coating material dries in the air (spray drying) and can then be lost in the exhaust air stream. Thus it never reaches the tablets and the CPE is again reduced. The CPE can be defined as the ratio of the actual weight gain to the theoretical weight gain, reported as percent,

$$\text{CPE} = \frac{\Delta ma}{\Delta mt} * 100 \qquad \text{..... (1)}$$

Where, Δma is the measured weight gain of all tablets together

Δmt is the theoretical weight gain

Δmt is calculated from the content of solid substances that coating suspension holds and from the total amount of coating suspension that is applied during the coating process.

2.8 INTRODUCTION TO DESIGN OF EXPERIMENTS [26]

- It is the method of how to conduct and plan experiments in order to extract the maximum amount of information in the fewest number of runs.
- The trial and error method require greater efforts and time, especially where complex formulations are to be developed. Factorial designs are used in experiments when the effects of different factors or conditions, on experiment results is to be explained. Factors may be qualitative or quantitative. The levels of an each factor are the value or designation assigned to combination of all levels of all factor. The effect of a factor is the change in response caused by varying the levels of the factor. The full factorial design is designated by following nomenclature;

$$N=L^K \quad \ldots\ldots (2)$$

Where; K = number of variables, L = number of variables levels, N = number of the experimental trials.

- The main objective of factorial design is to characterize the effect of changing the levels of the factor or combination of factors on the response variable. Predictions based on the results of an undesired experiment will be more variable than those, which could be obtained in a designed experiment, in particular factorial design.
- The optimization procedure is done by an equation that describes the experimental results as a function of the factor levels. A polynomial equation can be constructed, where the coefficients in the equation are related to the effects and interaction of the factors. The equation constructed form 3n factorial experiment is in the following form.

$$Y = Bo = B1X1 + B2X2 \ldots\ldots\ldots\ldots BnXn + B12X1X2 + B1X12 + B22X22 \ldots Bmn \quad \ldots\ldots (3)$$

Where, Y= the measured response,

X = level of n^{th} factor

B1, B2, B12= the coefficients from the response of the formulation in design,

Bo= Intercept

- The magnitudes of the coefficients represent the relative importance of each factor. Once the polynomial equation has been established, an optimum formulation can be found out by grid analysis. With the use of computer a grid method can be used to identify optimum regions, and response surfaces may be depicted. A computer can calculate the response based on equation at many combinations of factor levels. The formulation whose response has optimal characteristics based on the experimenter's specification is then chosen.

3^2 FULL FACTORIAL DESIGN

- The three level design is written as a 3^k factorial design. It means that k factors are considered at 3 levels.
- These are referred to as low, intermediate and high levels that are numerically expressed as -1, 0 and +1.
- The reason that three level design was proposed to model possible curvature in response function and to handle the case of nominal factors at 3 levels.

2.9 INTRODUCTION TO 11AD

Drug	β-Blocker
Indication	Cardio selective β1-adrenergic blocking agent used for acute myocardial infarction (MI), Heart failure, Angina pectoris and mild to moderate Hypertension.
Bioavailability	50% due to first pass metabolism.
Molecular weight	652.81g/mol
Solubility	Freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane; and 2-propanol; practically insoluble in ethyl-acetate, acetone
Log p	1.72
Pka	9.67
Absorption	Rapid and complete from GIT
Half-life	3 to 7 hours
Dose	25mg, 50mg, 100mg
% Assay content	98.0 – 102.0 %

2.10 INTRODUCTION TO POLYMERS [27]

1.HYDROXY PROPYL METHYL CELLULOSE

Nonproprietary name

BP: Hypromellose

JP: Hydroxyl propyl methyl cellulose

PhEur: Hypromellosum

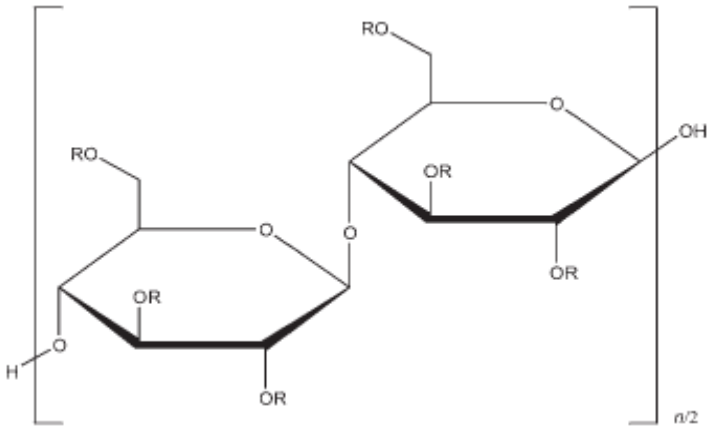
USP NF: Hypromellose

Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; TyloseMO.

Description: Odorless, tasteless, white to creamy white fibrous and granule powder.

Structural formula



Where R is H, CH_3, or CH_3CH (OH) CH2

Chemical name: cellulose, 2- hydroxyl propyl methyl ether

Molecular weight: 10, 000 to 15, 00, 000

Melting point: 170-180^{o}C (Glass transition temperature)

Solubility

Soluble in water, with a viscous colloidal solution. Practically insoluble in ethanol, chloroform and ether. But soluble in mixture of water and alcohol and mixture of ethanol and dichloromethane.

Functional categories

Suspending agent, tablet binder, viscosity enhancing agents, coating agent, film former and rate controlling polymer for sustained release.

Pharmaceutical applications

- In topical and oral formulation.
- Primarily used as
    - Binder (2-5%)
    - In film coating (2- 20%)
    - In extend release matrix (10-80%)
    - As thickening agent (0.45-1%) in eye drops.

Typical properties

pH: 5.5 - 8 (2% w/w aqueous solution)

Bulk density: 0.341 g/cm^3

Tapped density: 0.557 gm/ cm^3

Stability and storage condition

It is stable, though hygroscopic after drying.

Should be stored in well closed container in cool and dry place.

Incompatibilities

With oxidizing agent.

2.MICROCYSTALLINE CELLULOSE

Nonproprietary Names

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

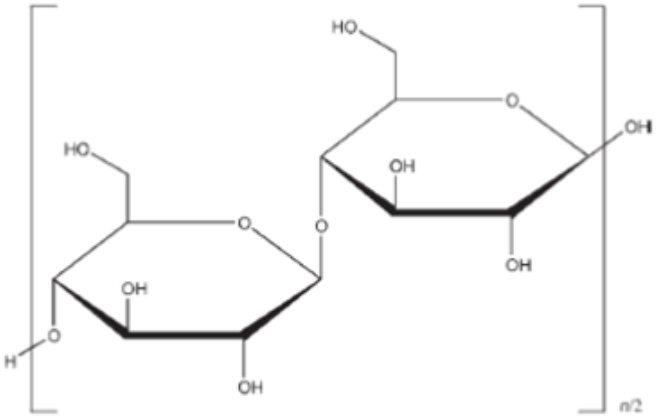
Synonyms

Avicel PH; Cellets; Celex; cellulose gel; hellulosummicrocristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur

Description

Purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Structural formula:



Chemical name: Cellulose

Molecular weight: 36000

Melting point: Chars at 260–270ºC

Solubility

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Functional categories: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant

Pharmaceutical Application

- As a binder/diluent in oral tablet and capsule formulations in both wet-granulation and direct-compression processes.
- Lubricant and disintegrant

Typical properties

Moisture content is less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

Stability and storage condition

Stable though hygroscopic material.

Should be stored in a well-closed container in a cool, dry place.

Incompatibilities:
Incompatible with strong oxidizing agents.

3. POLYVINYL PYROLIDONE

Nonproprietary name

BP: Povidone

JP: Povidone

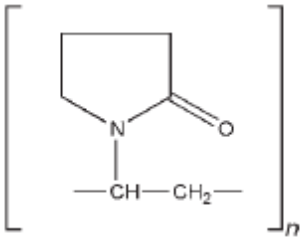
PhEur: Povidone

USP: Povidone

Synonym: E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1-vinyl-2-pyrrolidinone polymer

Description: Fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

Structural formula



Chemical name: 1-Ethenyl-2-pyrrolidinone homopolymer

Molecular weight: 2500–3000000

Melting point: Softens at 150^0C.

Solubility

Freely soluble in chloroform, acids, ethanol (95%), methanol, ketones and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Functional categories

Disintegrant; dissolution enhancer; suspending agent; tablet binder.

Pharmaceutical Application.

- As binders in wet-granulation processes.
- Added to powder blends in the dry form and granulated in situ by the addition of water, alcohol or hydro alcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.
- As coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads.
- As a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions.

Typical properties

Moisture content: Povidone is very hygroscopic, significant amount of moisture being absorbed at low relative humidities.

Stability and storage condition

Darkens to some extent on heating at $150^{O}C$, with a reduction in aqueous solubility. Aqueous solutions are susceptible to mold growth and consequently require addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals.

It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thiomersal, may be adversely affected by the formation of complexes with Povidone.

4. MANNITOL

Nonproprietary name

BP: Mannitol

JP: D-Mannitol

PhEur: Mannitol

USP: Mannitol

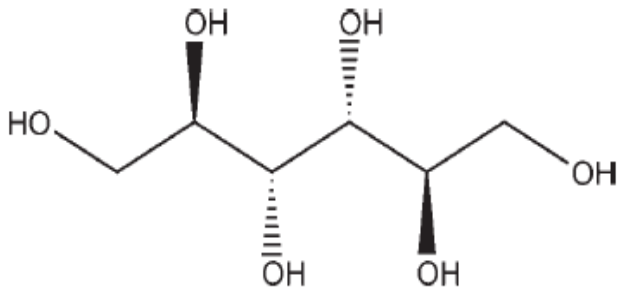
Synonyms

Cordycepic acid; C*PharmMannidex; E421; Emprove; manna sugar; D-mannite; mannite; mannitolum; Mannogem; Pearlitol.

Description.

- It is a hexahydric alcohol related to mannose and is isomeric with sorbitol.
- Mannitol occurs as a white, odorless, crystalline powder, or freeflowing granules.
- It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth.
- Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

Structural formula



Chemical name: D-Mannitol

Molecular weight: 182.17

Melting point: 166–168^{0}C

Solubility: Mannitol is soluble in alkalis and insoluble in ether

Functional categories

Diluent; plasticizer; sweetening agent; tablet and capsule diluent; therapeutic agent; tonicity agent.

Pharmaceutical application

- As a diluent (10–90% w/w) in tablet formulations
- Used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations.
- Excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel.
- In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial.
- Plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations and as a carrier in dry powder inhaler.
- It is also used as a diluent in rapidly dispersing oral dosage forms.
- It is used in food applications as a bulking agent.

Typical properties

Stability and storage condition

Mannitol is stable in the dry state and in aqueous solutions. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.

Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.

Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.

CHAPTER - 3

LITERATURE REVIEW

3. LITERATURE REVIEW

3.1 REVIEW OF WORK DONE OF API COATING ON TABLETS

1. **Wang J et al** [15] carried out evaluation of various process parameters affecting coating efficiency of an active film coating process taking 24 batches having different core tablet sizes, weights and shapes. Computational fluid dynamics modeling of the droplets showed reduced fraction of smaller droplets, especially those smaller than 10µm, resulting in a marked improvement in the coating efficiency while other variables like duration of coating, pan speed, solid concentration, tablet velocity and exhaust air temperature did not affect the coating efficiency. It was concluded that controlling the coating liquid delivery process is the most effective way to improve the efficiency of an aqueous tablet active film coating in a perforated pan coater. Higher ratio of suspension spray rate/atomization air flow rate, atomization air flow rate/pattern air flow rate and suspension spray rate/ pattern air flow rate had positive impact on coating efficiency.

2. **Rege B et al** [28] described various process variables that affect content uniformity and loading of active agent on tablet using Placket and Burman design. The process variables that influence the content uniformity were inlet airflow, pan speed, inlet air temperature, coating time, atomization pressure and fan pressure. Here 24" Accela-Cota a side vented coating pan was used to spray the coating solution onto the core tablets. HPMC and Polyethylene glycol (PEG) were used as coating solution to be sprayed on 800 mg oval biconvex tablets. F, D & C Yellow #6 dye was chosen as a surrogate marker for a water soluble active constituent which was easily analyzed by UV visible spectroscopy. Fan Pressure was identified as the most critical variable affecting recovery. It was concluded that the major factors which affects the coating uniformity are atomization pressure, pan speed and coating time. It was possible to achieve %RSD of less than 6% while maintaining the recovery at 80% or higher.

3. **Just S et al** [18] described inter tablet coating uniformity by optimizing various process parameters for coating Candesartan Cilexetil on Nifedipine tablets for preparing fixed dose combination with different release profile. Candesartan cilexitil and polyvinyl alcohol based lacquer (Opadry® II 85F clear) were incorporated in the coating solution. At lab scale the parameters like pan speed, pan load, spray rate and number of spray nozzles were evaluated by conducting two 2^3 full factorial screening design, wherein the first DOE batch was run with two spray nozzle and the second DOE was run with four spray nozzles. At pilot scale, parameters like pan speed, pan load, spray time, spray rate and spray pressure were investigated using 2^{5-1} fractional factorial design having 16 runs. At pilot scale the CV values between 2.7% and 11.1% were achieved. It was concluded that low spray rate and high pan speed improved coating efficiency. Moreover it was observed that number of spray nozzles is an influencing variable affecting content uniformity.

4. **Chen W et al** [29] gave an engineering model for prescribing API content uniformity wherein the active is coated onto a core tablet of various shapes and sizes. A mathematical model based on two zone concept using Residence time distribution (RTD) theory as a basis for estimating % Relative standard deviation (RSD) of coated tablets was established. Tablet velocity, tablet number density and spray zone width were integrated in this model. The sensitivity of the RSD to critical process parameters like pan load, pan speed, spray zone width and tablets shape and size were evaluated. Several film active coating experiments at 50, 200 and 400 kg using various pan coaters demonstrated good correlation between the model predictions and experimental results for the API Content uniformity was achieved. A good correlation was achieved between mechanistic model and experimental data. It was concluded that as CU is a function of spray coating time, the spray rate can be selected accordingly for the desired % RSD by balancing the CU and efficiency of the coater.

5. **Kim J et al** [30] carried out a study to formulate fixed dose combination tablets (FCTs) of Glimepride (GLM) immediate release (IR) layer on Metformin Hydrochloride (MTF) extended release (ER) core tablet using perforated film coating equipment. Glimepride is a sulphonylureaantidiabetic drug also acting as secretagogue given once daily and MTF a biguanideantidiabetic drug given more than twice daily. Combination of MTF and Glyburide showed improved patient compliance in treatment of diabetes. There is a need for fixed dose combination of GLM (immediate release) and MTF (extended release) for increasing the patient compliance. Hence due to this reason, new technology consisting of the immediate layer in the coating solution was applied to core extended release tablet to prepare fixed dose combination. The Near Infrared Spectroscopy (NIR) an analytical tool was used to determine the end point of the coating process. Composition of Glimepride coating suspension with ratio of SLS-GLM at 0.75 was studied for homogeneity. The new fixed dose combination comprised of three layers. (1) an MTF core tablet (2) an inert mid layer (3) an outer GLM-IR layer. An inert mid layer was necessary to be kept between the two layers of the drug in order to avoid the contact with each other and this helped to increase the release rate of GLM in pH medium of 7.8. The final product was administered to the male volunteers and the pharmacokinetic parameters of GLM in FCT's were confirmed to be bioequivalent to the marketed product.

6. **Desai D et al** [31] patented a coated tablet formulation containing PPAR α/γ dual agonist Peliglitazar or Muraglitazar used to lower glucose and lipid levels and thus useful for treatment of Type II diabetes and dyslipidemia containing binder, filler, disintegrant and other conventional excipients in the core and one or more layer of coating which was formed of one or more coating polymer preferably Hydroxypropoxy methylcellulose (HPMC) based polymer. Moreover Peliglitazar undergoes acid and base catalyzed hydrolysis. Capsules were formulated to avoid base catalyzed hydrolysis but the problem was not completely solved. To circumvent this, dry and wet granulation formulations were prepared with addition of pH modifiers such as citric acid. Dry granulation showed acid degradation while the wet granulation formulation showed loss of potency at accelerated conditions. In this invention, the coating layers were applied using spray

coating technique and Opadry Orange (HPMC base). Second coating layer containing medicament was coated over the initial coating layer and functions as protective layer. The main advantage over other techniques is it is a single unit operation and helps to reduce the cycle time.

7. **Solomonowich R et al** [32] prepared a pharmaceutical dosage form comprising of compressed inert core, an optional sub coat and a drug layer over compressed core. Rivaroxaban a water insoluble drug having anticoagulant activity is used. Methods like wet granulation, dry granulation, melt processing involved undesirable steps that raise significant disadvantages, and hence it was desirable to provide composition that can be easily manufactured by a simple process wherein the risk of product degradation in avoided. The inert core of the tablet comprises of filler, binder, and lubricant. The drug incorporated in the coating layer was in micronized form and the coating solution comprises of fully formulated pharmaceutical film coating system such as Opadry® coating system. The dispersion is then sprayed over inert core tablets using pan coater. It was found that layered compositions of the present invention were able to achieve good release rate and bioavailability of the drug without the need to use the pseudo emulsifiers.

3.2 REVIEW OF WORK DONE OF AQUEOUS FILM COATING ON TABLETS

1. **Savkare A et al** [33] evaluated and optimized tablet film coating process using Pharma coater based on general pan coating principle. Critical process parameters determined were targeted to optimize the coating process. The results of preliminary trials showed that inlet air temperature (X1), pan rotation speed (X2) and spray rate (X3) as the critical process parameters that affected the tablet coating process. 2^3 full factorial design was used to optimize the above three critical process parameters as independent variables with responses as weight deviation (standard deviation) [R1] and coating process efficiency [R2] as dependent variables. Thus, the coating process optimization was done to set the coating parameters for coating of any strength of tablet batch. The inlet air temperature at 55°C, rotating speed of pan rotation of 2 rpm and spray rate of 12 ml/min gave the

optimum results of the coating process favoring the responses as weight gain and efficiency of coating process.

2. **Sheth N et al** [34] studied the aqueous based film coating of tablets using laboratory scale side vented perforated pan coating apparatus. The tablets were evaluated for coating uniformity (mg), coating process efficiency (%), surface roughness and loss on drying. The process parameters relevant to a side vented perforated pan coating process was identified and optimized. Spray rate and inlet air temperature both affected all characteristics of coated tablets. Pan speed were identified as the main parameter affecting coating uniformity of tablets. Lower spray rate led to rough surface and higher spray rate caused sticking and picking. Higher rotating speed of the pan improved mixing of the tablets and distribution of coating solution onto the tablet bed. At higher atomizing air pressure small droplets were formed and at lower pressure big droplets were formed which affected the coated tablets.

3. **Jason T et al** [35] optimized process parameters and an acceptable operating space for film coating with Opadry®200. Three sets of coating process parameters were identified as being acceptable from the pilot scale work in 24" diameter fully perforated O'Hara Labcoat II coating pan on scale in a 48" diameter coating pan to confirm the suitability. The environment efficiency factor (EEF) was identified using a thermodynamic modeling program for each scale at pilot scale. Coating of Opadry 200 was successfully scaled up through the use of pilot scale process parameters and a thermodynamic model to determine process parameters that offer equivalent drying conditions at production scale. Color Uniformity, Coating productivity and very low defects were obtained with Opadry 200 even when using a broad range of coating process conditions and coating scales.

4. **Ratnaparkhi M et al** [4] described the study of coating formula and aqueous based film coating of tablets prepared by wet granulation technique utilizing laboratory scale side vented perforated pan coating apparatus. Critical process parameters like atomizing air pressure and inlet air temperature and were optimized using 3^2 full factorial designs,

Design expert version software was used to study the effect of independent variables like atomizing air pressure and inlet air temperature on dependent variables like sticking and picking, orange peel effect, surface roughness, coating process efficiency. It was concluded that optimization of atomizing air pressure, inlet air and temperature showed desired coating on the tablets.

5. **Siepmann J et al** [36] reviewed various mathematical models to describe drug release from hydroxypropylmethylcellulose (HPMC)-based pharmaceutical devices. The major advantages of these models were: (i) the elucidation of the underlying mass transport mechanisms; and (ii) the possibility to predict the effect of the device design parameters (e.g., shape, size and composition of HPMC-based matrix tablets) on the resulting drug release rate, facilitating the development of new pharmaceutical products. Higuchi equation and power law and complex mechanistic theories that consider swelling, diffusion and dissolution processes simultaneously were presented with their advantages and limitations. The choice of appropriate mathematical model depends on the desired predictive ability and accuracy of model when developing new pharmaceutical products or elucidating drug release mechanisms strongly.

3.3 REVIEW OF WORK DONE ON COATING UNIFORMITY AND COATING EFFICIENCY

1. **Tobiska S et al** [37] examined the influence of tablet size, batch size, pan speed and inclination of the rotation axis on the coating uniformity and efficiency in a Bohle Lab-Coater BLC 5. The coating uniformity was evaluated using the mass variance, the dissolved amount of Acetaminophen after 2 h in Hydrochloric acid pH 1.0 at a polymer loading of3 mg/cm^2 and the minimum amount of polymer for an enteric coating. Increase in pan speed was observed with decrease in mass variance of final tablets. Linear and quadratic effect were seen in case of small oval tablets and a linear effect for large tablets. The minimum amount of polymer required for gastric resistance depends on the pan speed for both tablet sizes. The dissolved amount of acetaminophen after 2 h in simulated gastric fluid was influenced linearly by the batch size for both kind of tablets. In case of large oval tablets it was also influenced by the pan speed, batch size and

inclination of the rotation axis. Increase in pan speed and batch size led to increase in dissolved amount of acetaminophen.

2. **Dubey A et al** [38] carried out computational study using the discrete element method to study the effect of pan speed, fill level and design of the spray pattern using a rotating pan on coating variability of tablets. Movement of tablets in pan was simulated with method and the residence time of each tablet inside the spray zone was calculated. Laser induced breakdown spectroscopy based analytical method was used to validate the computational method. The simulations showed that axial mixing was the most critical parameter affecting the coating variability, though it did not affect the coating variability significantly. 100% fill level was used as compared to 67% fill as lower variability was obtained. Two idealized (full surface spray and a symmetric band spray) and two realistic (5-ellipse and 5-circular) spray guns were used. Ellipse and circular pattern were similar to each other while full and band spray showed similar results while at all speeds and fill levels.

3. **Sahni E et al** [39] investigated the effect of the coating process parameters on coating variability and coating performance and determined the optimal operating conditions. The coating solution was sprayed in specific locations of the granular bed and coating uniformity was achieved by overall mixing behavior in the coater and interparticle collisions. The aqueous solution of Opadry II was sprayed intermittently at different concentration and flow rates. Vernier Caliper was used to measure the change in diameter and the coating of the particles. DEM based numerical modeling of spray coating was also performed for same operational parameter set and spray characteristic (center and the radius of the spray zone) used in the experiments. The coating variability was estimated at different pan and spray variables. Increase in pan tilt, coating time and an optimum speed led to decrease in coating variability. Better coating is observed under better mixing conditions of high tilt and pan speed for the same spray parameters. The spray characteristics does not have much effect on the variability.

4. **Daniele S et al** [40] carried out a study to analyze and understand the effects of tablet form and fill volume on the intra-tablet coating variability in a semi-continuous coating device. Three different shapes namely biconvex, oval and round were modeled by means of glued spheres. A detailed analysis of tablet velocities both rotational and translational on top of the tablet bed was presented. Numerical simulation via DEM (discrete element method) improved an understanding of tablet mixing inside a real continuous coater and helped to optimize a design space for operation of this device.

5. **Dubey A et al** [41] described improvement in the tablet coating process applying QbD (Quality of Design) principles by using combination approach of analytical and statistical methods. The effect of amount of coating material, spray rate, pan rotation and spray temperature using Response surface modeling and Kriging method was studied to arrive at an optimal set of operating conditions. The results were quantified analytically in terms of relative standard deviation of tablet averaged – LIBS (Laser induced breakdown spectroscopy) and from the ratio of standard deviation of tablet-averaged LIBS-score and weight gain of the tablet known as coating variability index. Minimum value of this index was achieved for a pan rotating at a higher speed for maximum fill levels at lowest spray rate and temperature from the parametric space at a 6% weight gain. The observations made at the end of the result indicated that the tablet to tablet (within a lot) variability was due to mixing limitations in the coating pan and could be avoided in the future. It was concluded that variance was reduced by more than half by optimizing the coating composition, coating thickness and coating process parameters.

CHAPTER - 4

EXPERIMENTAL WORK

4. EXPERIMENTAL WORK

4.1 MATERIALS USED:

Table 4.1: List of materials used

MATERIALS	CATEGORY	COMPANY NAME
CORE TABLETS		
Microcrystalline cellulose (Avicel PH101)	Diluent	FMC Biopolymers, Wallingstown, Ireland
Mannitol (Pearlitol SD 200)	Diluent	Roquette, France
Polyvinyl Pyrolidone (PVP K 30)	Binder	BASF Corporation, Germany
Magnesium stearate	Lubricant	Ferro Corporation, Cleveland.
COATING SOLUTION		
11AD(API)	Active Pharmaceutical Ingredient (API)	Aarti Drugs Limited, Thane, India.
HPMC E5	Film Former	Dow chemicals Ltd, Germany

4.2. EQUIPMENT'S USED:

Table 4.2: List of equipment's used

EQUIPMENTS	MODEL NO	COMPANY NAME
Analytical electronic weighing balance	ML204	Mettler Toledo, Switzerland
Industrial balance	BBA 422 – 6 SM	Mettler Toledo, Germany
Rapid mixer granulator	HSMG – 10	Ganson, Thane, India
Fluidized bed drier	TG 200	Retsch, Hyderabad, India.
Moisture analyser	HG 63 Halogen	Mettler Toledo, Mumbai, India
Sieve shaker	AS 200 Tap	Retsch, Germany
Tap density tester	TD 1025	Labindia, Thane, India
16 station punching machine	CDM4	Cadmach, Ahmedabad, India
Roche friabilator	FT020	Labindia, Thane, India
Hardness tester	8M	Dr. Schleuniger Pharmatron 8M, Switzerland
Digital vernier callipers	DTH-250	Thermonik Tablet Tester
Turbula blender	T2F	WAB, Switzerland
Conta blender	12 L	STM, Mumbai, India
Magnetic stirrer with hot plate	-	Deepali, India
Comill	-	Quodro Engineering, Canada
Overhead stirrer	RQ – 122	Remi Motors
Tablet coater	GAC-250	Ganson, Thane, India
UV spectrophotometer	Double beam 1800	Shimadzu, Japan
FTIR	6100 TGS	Jasco, Japan
Optical microscope	CH20iBIMF	Olympus, Noida, India

4.3. IDENTIFICATION OF 11AD

4.3.1 Melting Point Determination: [42]

Melting point is the temperature at which pure liquid and solid exist in the equilibrium. It is taken as equilibrium mixture at an external pressure of 1 atmosphere; this is referred as normal melting point. The Thiel's tube method of melting point determination in liquid paraffin was used in the present study. Melting point was found to be 136 °C.

Figure 4.1: Thiel's tube for determination of melting point

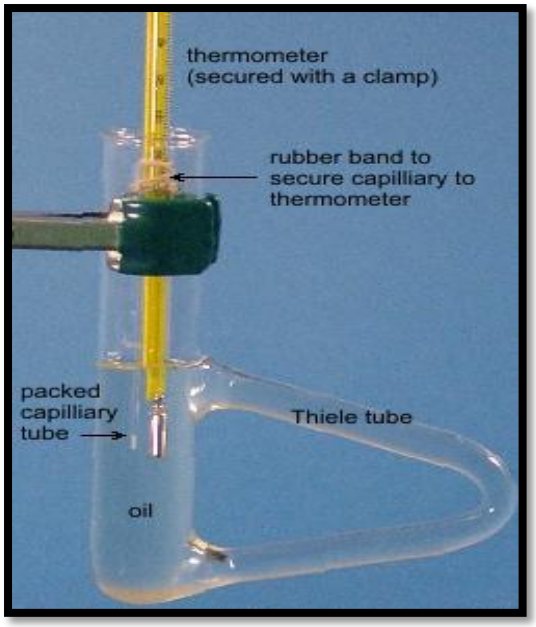


Table 4.3: Melting Point Determination of 11AD

Reported melting point	Observed melting point
135-137°C	136°C

Result and Discussion: The melting point of the β-Blocker drug was found to be 136°C. The melting point determined is within the range of standard value, hence, it is concluded that the drug sample having similar physical property as standard drug.

4.3.2 FTIR Spectra: [43]

IR spectra of drug was carried out using KBr pellets at moderate scanning speed between 4000-400 cm-1 FTIR. All the powder samples were dried under vacuum prior to obtaining any spectra in order to remove the influence of residual moisture.

Figure 4.2: Reference FTIR Spectra of 11AD [43]

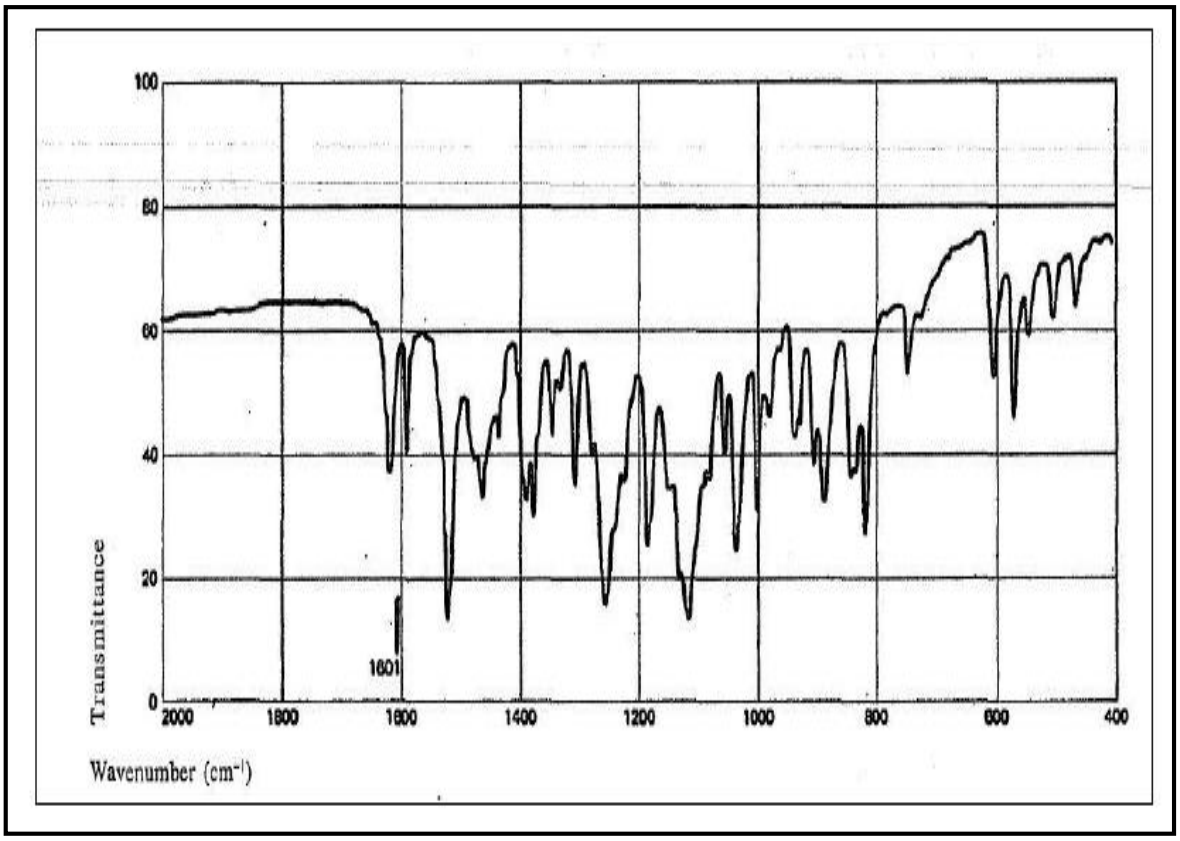


Figure 4.3: Test Spectra of 11AD

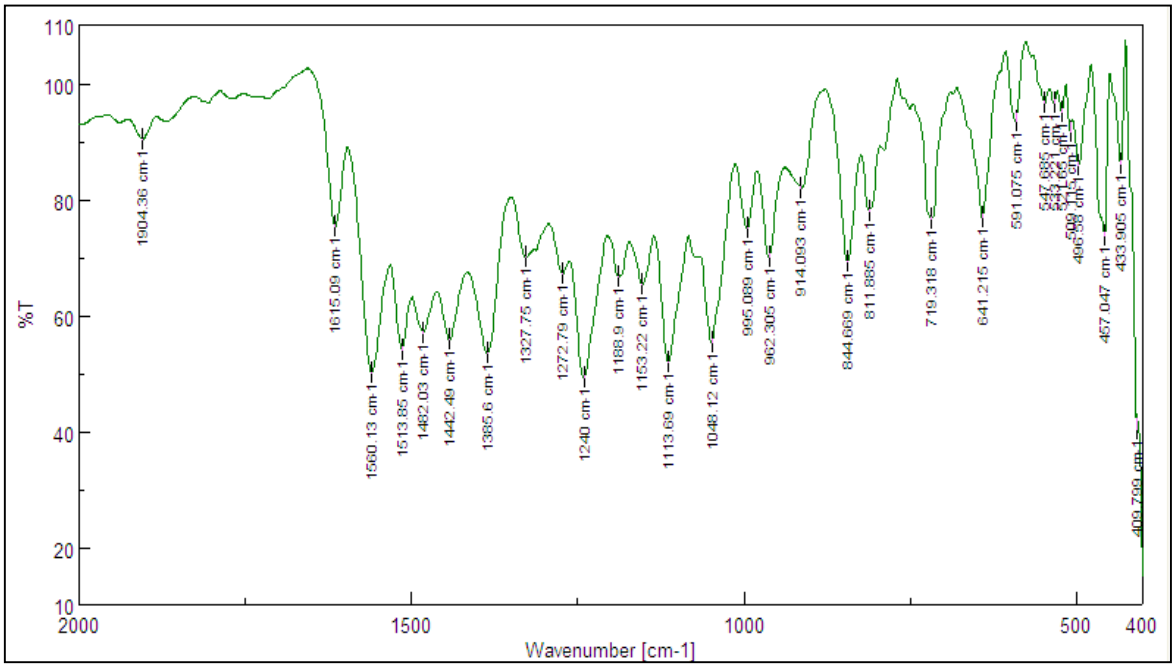


Table 4.4: Comparison of Reference and Test IR Frequency of 11AD

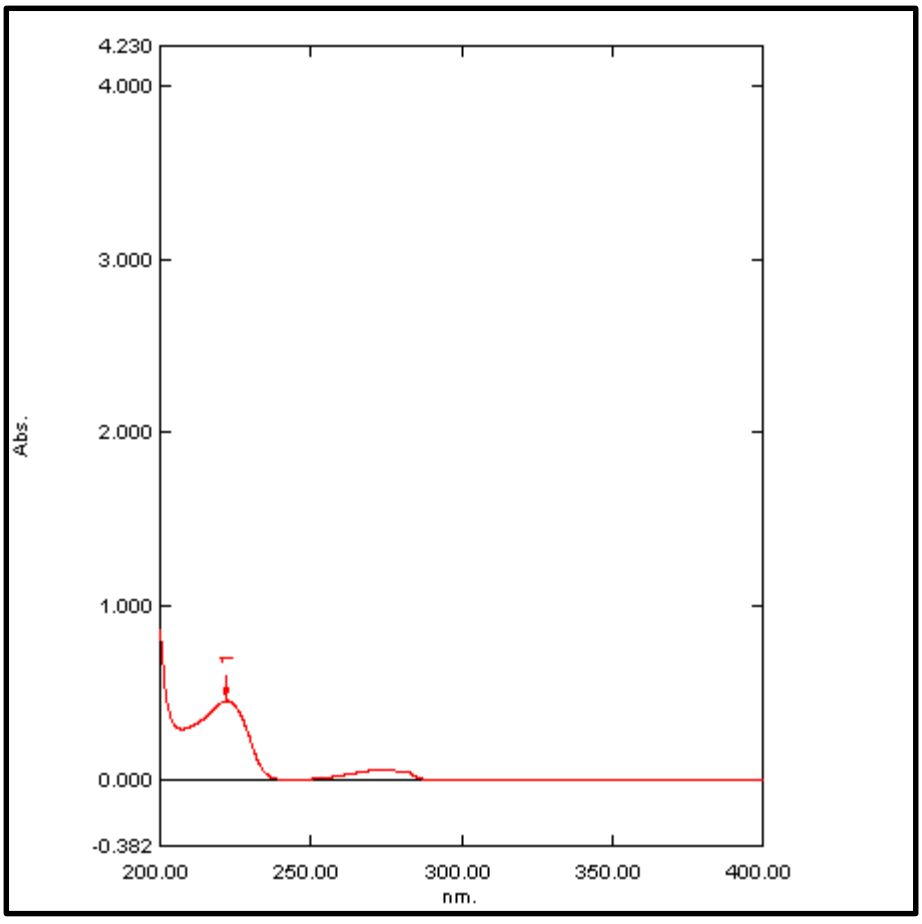
Functional group	**Standard frequency (cm^{-1})**	**Observed frequency (cm^{1})**
Benzene stretching	1618.00	1615.09
N-H bending	1583.00	1560.13
C-O stretching in C-O-C	1110.84	1113.69
C=O	1245.00	1240.00
C-OH stretching(1°Alcohol)	1045.52	1048.12
C-O stretching in C=C-O-C	1238.39	1240.00

Result and Discussion: According to the assigned functional group in molecular structure relevant peaks were obtained. No other non-relevant peaks were observed so it can be concluded that the given drug sample is pure.

4.3.3 UV Absorbance Spectra in Distilled Water:

11AD was accurately weighed equivalent to 100 mg and transferred into a 100 ml volumetric flask and then volume was made up using distilled water to concentration of 1000 µg/ml. From the above stock solution (1000 µg/ml), 1.5 ml was transferred to 100 ml volumetric flask and volume was made up with distilled water. The resultant solution was scanned in the range of 200 nm to 400 nm using Shimadzu double beam UV/Visible spectrophotometer.

Figure 4.4: Absorbance spectra of 11AD in distilled water



Discussion: The absorption maxima was found to be 222 nm and the absorbance value was 0.456.

4.3.3.1 Establishment of calibration curve of 11AD in Distilled Water:

Dilution of stock solution:

From the stock solution (1000 µg/ml), serial dilutions were made by taking 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml drug solution in 100 ml volumetric flask, dissolved in distilled water to make up the volume and produce concentration range to give 5, 10, 15, 20, 25 µg/ml concentration respectively. The absorbance of diluted solution were measured at λmax= 222 nm using Shimadzu double beam UV/Visible spectrophotometer in triplicate and the plot of average absorbance vs. concentration was established.

Figure 4.5: Overlay spectra of 11AD in distilled water

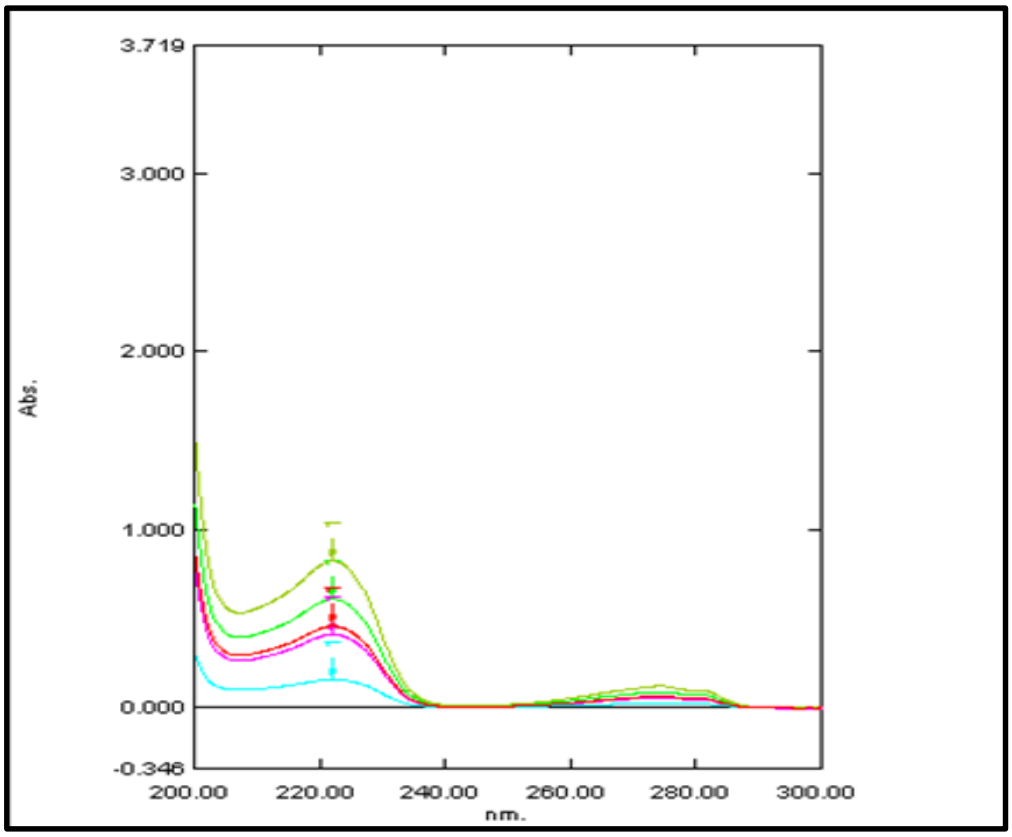


Table 4.5: Calibration curve of 11AD in distilled water

Concentration (µg/ml)	Absorbance			Average Absorbance (n = 3) ± Standard Deviation
	1	2	3	
0	0	0	0	0
5	0.155	0.154	0.156	0.155 ± 0.001
10	0.309	0.307	0.308	0.308 ± 0.001
15	0.456	0.452	0.458	0.455± 0.003
20	0.621	0.626	0.624	0.623± 0.002
25	0.79	0.781	0.792	0.787± 0.005

Figure 4.6: Calibration curve of API in distilled water

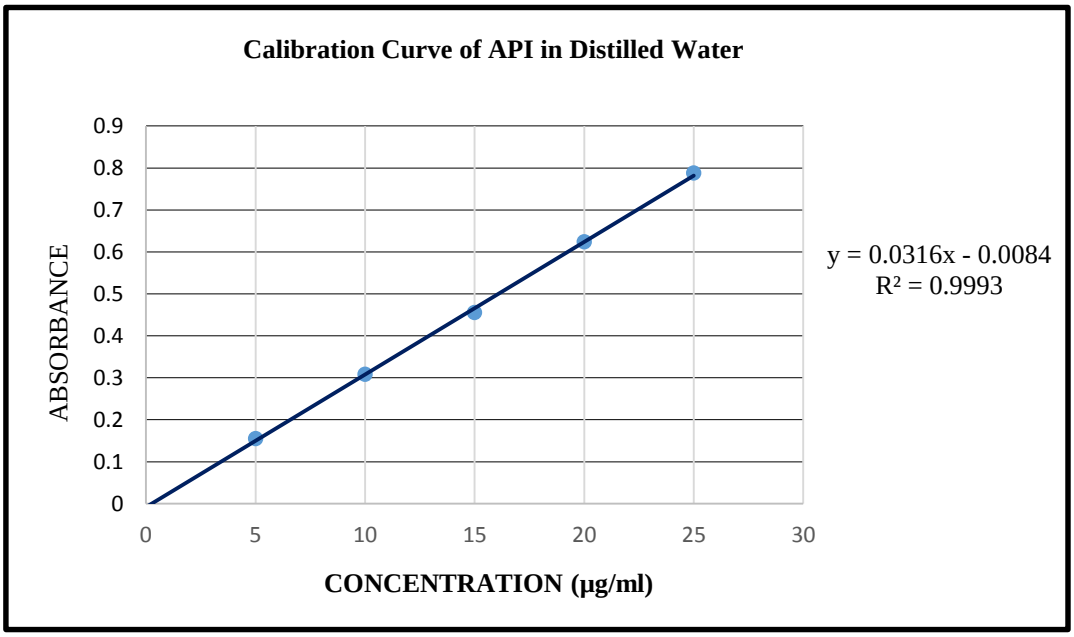


Table 4.6: Regression Analysis for Standard Curve of 11AD in Distilled Water

Regression Parameters	Values
Correlation Coefficient	0.9993
Slope	0.0316
Intercept	0.0084

Result and Discussion:

0 - 25 µg/ml concentration of drug solution was made. The UV spectra of 11AD showed λmax at 222 nm. Linear graph with r^2 value of 0.9993 was obtained which obeys Beers lambert law.

4.4 METHODOLOGY

4.4.1 Evaluation of tablet blend [44, 45]

1. Bulk Density (D_b):

It is the ratio of total weight of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder of 100 ml and the volume was noted. It is expressed in g/ml and is given by

$$Db = \frac{M}{V0} \qquad \text{..... (1)}$$

Where, *M* is the mass of powder, V_0 is the Bulk volume of the powder.

2. Tapped Density (D_t):

Tap density was measured by Tap density tester (TD1025). It is the ratio of total weight of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$$Dt = \frac{M}{Vt} \qquad \text{..... (2)}$$

Where, ***M*** is the mass of powder, ***Vt*** is the tapped volume of the powder.

3. Angle of Repose (θ):

The frictional forces in a loose powder can be measured by the angle of repose, θ. The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

$$\tan\theta = \frac{h}{r} \qquad \text{..... (3)}$$

Where, ***h*** and ***r*** are the height and radius of the powder cone.

Table 4.7: Angle of Repose

Sr. No	Angle of Repose	Type of Flow
1	25-30	Excellent
2	31-35	Good
3	36-40	Fair- aid not needed
4	41-45	Passable – may hang up
5	46-55	Poor – must agitate, vibrate
6	56-65	Very poor
7	>66	Very, very poor

4. Hausner's ratio (H):

Hausner's ratio is the ratio of tapped density to bulk density

$$H = \frac{Dt}{Db} \qquad \text{..... (4)}$$

Where,***Dt*** and ***Db*** are tapped density and bulk density respectively.

Table 4.8: Hausner's ratio

Hausner's Ratio	Type of flow
<1.25	Good flow
>1.25	Poor flow

5. Carr's Index (I):

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I = \frac{Dt-Db}{Dt} \quad \text{...} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Where, ***Dt*** is the tapped density of the powder,***Db*** is the bulk density of the powder

Table 4.9: Carr's Index

Sr. No	Carr's Index	Type of Flow
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-25	Poor
5	33-38	Very poor
6	>40	Very very poor

4.4.2 Tablet characteristics:

1. Weight variation test:

To study weight variation twenty tablets of the formulation were weighed using a Metler Toledo electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation

Table 4.10: Limit for weight variation as per USP [46]

Dosage form	Average weight	Percentage deviation
Uncoated and film coated tablets	≤ 130 mg	± 10 %
	130 – 324 mg	± 7.5 %
	>324 mg	± 5 %

2. Hardness:

Hardness of the tablets was measured using hardness tester (Dr. Schleuniger Pharmatron, 8M). It is expressed in kilopond (Kp).

3. Thickness:

The thickness of the tablets was determined by using Digital Vernier Calipers (Thermonik Tablet Taster, DTH – 250). It is expressed in mm.

4. Friability Test:

The friability of the tablet was determined using Roche Friabilator (LabIndia, FT020) It is expressed in percentage (%). Friability is usually determined by tumbling 6.5 g or more of tablet weight for a set number of rotations inside a friabilator which is usually 100 revolutions. Here as the tablets need to be coated the friability is also done for 300 and 500 counts.

$$\% \text{ Friability} = \frac{W(\text{initial}) - W(\text{final}) * 100}{W(\text{initial})} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

Where, ***W (initial)*** is the initial weight of tablets and ***W (final)*** is the final weight of tablets

5. Content Uniformity:

Methodology: The test for Content Uniformity is based on the assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual content is within the limits set. 10 tablets were assayed individually and dissolved into 10 different 200ml volumetric flask. Then 100ml distilled water was added to dissolve the tablet and sonicated for 15 min. The volume was made up with the distilled water and filtered through 0.45µm PVDF filter and absorbance was measured at 222nm.

Table 4.11: Calculation for Acceptance value [23]

Variable	Definition	Condition	Value
$\bar{x}$	Mean of individual contents ($\chi 1$, $\chi 2$, … , χn), expressed as a per- Percentage of label claim		
$\chi 1$, $\chi 2$, … , χn	Individual contents of the units tested, expressed as a percentage of label		

	claim		
n	Sample size (number of units in a sample)		
k	Acceptability constant	If n = 10, then k =	2.4
		If n = 30, then k =	2.0
s	Sample standard deviation		
RSD	Relative standard deviation (the sample standard deviation expressed as % of mean)		100s/ $\bar{x}$
M (case 1) to be applied when T≤101.5	Reference value	If 98.5% ≤ $\bar{x}$ ≤101.5%, then	M = $\bar{x}$ (AV = ks)
		If $\bar{x}$<98.5%, then	M = 98.5% (AV = 98.5 – $\bar{x}$ + ks)
		If $\bar{x}$ >101.5%, then	M = 101.5% (AV = $\bar{x}$ – 101.5 + ks)
M (case 2) to be applied when T M = X	Reference value	If 98.5 ≤ $\bar{x}$ ≤T, then	M = $\bar{x}$ (AV = ks)
		If $\bar{x}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\bar{x}$ + ks)
		If $\bar{x}$ >T, then	M = T% (AV = $\bar{x}$ – T + ks)
Acceptance value (AV)			$/\mathbf{M} - \bar{\mathbf{x}}/+ \mathbf{ks}$ (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance		L1 = 15.0 unless otherwise specified
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	On low side, no dosage unit result can be less than [1 (0.01) (L2)] M, while on high side no dosage unit result can be greater than [1 + (0.01) (L2)]M. (This is based on an L2 value of 25.0.)	L2 = 25.0 unless otherwise specified
T	Target content per dosage unit at time of manufacture, expressed as a % of label claim, unless otherwise stated, T is 100 percent % or T is manufacturers approved target content per dosage unit		

Table 4.12: Risk assessment of process parameters affecting coating

Risk	Acceptability	Parameters
Low	Broadly acceptable risk. No further investigation is needed	• Inlet / exhaust temperature
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk.	• Gun to bed distance • Aperture size of gun • Bed temperature
High	Risk is unacceptable. Further investigation is needed to reduce the risk	• Coating time • Atomization pressure • **Pan load** • **Pan speed** • **Spray rate**

4.5 FORMULATION DEVELOPMENT

4.5.1 Composition of core tablets:

Table 4.13: Weight and Punch size of different shaped tablets

Sr. No	Shape	Weight	Punch size (D tooling)
1	Round	200 mg	7.5 mm Standard concave punch
2	Oval	200 mg	10 * 5.5 mm Standard concave punch
3	Round	600 mg	11 mm Standard concave punch
4	Oval	600 mg	16.5 * 7.5 mm Standard concave punch

Table 4.14: Composition for trial of Core Tablets

Total No. of tablets			1	4000	1	1334
Sr. No	**Ingredients**	**% w/w**	**qty/200 mg tablet (mg)**	**qty/800 g batch (g)**	**qty/600 mg tablet (mg)**	**qty/800 g batch (g)**
	Intra granular					
1	MCC (Avicel PH101)	77.00	154	616	462	616
2	Mannitol (Pearlitol 200 SD)	19.50	39	156	117	156
3	PVP K 30	2.50	5	20	15	20
4	Water	q.s	q.s	q.s	q.s	q.s
	Extra granular					
5	Magnesium Stearate	1.00	2	8	6	8
	Total Weight	100.00	200	800	600	800
* Here the quantity is mentioned for each batch containing 800 g pan load						

4.5.2 Method of manufacture:

The core tablets can be prepared by any of the conventional method:-

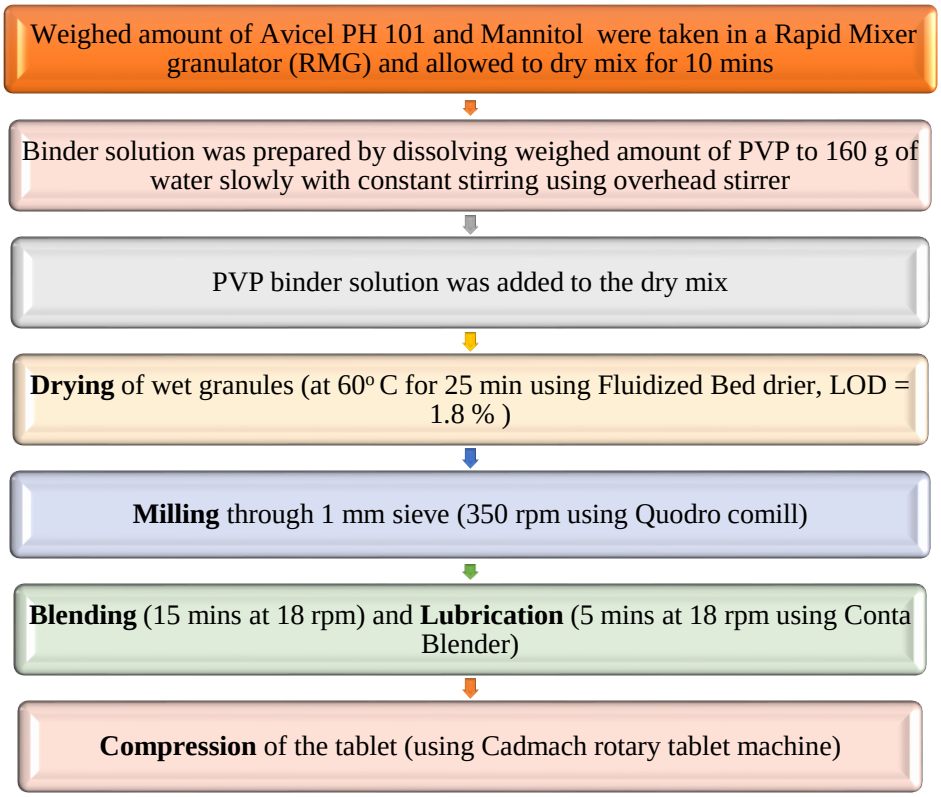
1. Direct Compression

2. Wet Granulation

3. Dry Granulation

Wet granulation approach was used based on availability of the excipients.

Figure 4.7: Wet Granulation Method for preparing core tablets



4.6 RESULTS OF THE CORE TABLETS

4.6.1: Evaluation of blend:

4.6.1.1: Flow properties:

Table 4.15: Powder Flow characteristics of Lubricated blend

Sr. No	Parameter	Value	Type of flow
1	Bulk density (g/ml)	0.5543	-
2	Tapped density (g/ml)	0.6502	-
3	Hausner's ratio	1.17	Good
4	Compressibility index	14.749	Good
5	Angle of repose (θ)	21.5	Good

Result and discussion: From evaluation of data for flow properties of the lubricated blend it was interpreted that lubricated blend had compressibility of 1.17, compressibility of 14.749, and angle of repose of 21.5 which showed good flow property as well as compressibility according to the limits specified in USP [42]

4.6.2. Results of tablet characteristics

4.6.2.1 Weight variation, thickness, diameter and hardness of 200 mg round tablets:

Table 4.16: In process quality control (IPQC) for 200 mg round tablets

Sr. No	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (kp)
1	202.3	3.96	7.48	12.6
2	201.5	3.97	7.48	13.2
3	200.3	3.96	7.47	12.7
4	201.5	3.96	7.49	13.2
5	201.9	3.97	7.48	12.8
6	200.3	3.95	7.49	12.4
7	200.5	3.96	7.48	14.0
8	201.5	3.96	7.47	13.6
9	201.4	3.97	7.48	12.8
10	200.4	3.97	7.49	13.7
Average	201.16	3.96	7.48	13.1
Minimum	200.3	3.95	7.47	12.4
Maximum	202.3	3.97	7.49	14.0

4.6.2.2 Weight variation, thickness, width, length and hardness of 200 mg oval tablets:

Table 4.17: IPQC for 200 mg oval tablets

Sr. No	Weight (mg)	Thickness (mm)	Width (mm)	Length (mm)	Hardness (kp)
1	202.1	3.91	4.96	9.95	13.8
2	202.3	3.93	4.97	9.96	13.6
3	200.6	3.93	4.96	9.95	12.7
4	201.7	3.92	4.97	9.95	13.9
5	200.1	3.91	4.96	9.96	14.0
6	200.2	3.93	4.97	9.97	13.4
7	200.3	3.92	4.97	9.96	13.0
8	201.1	3.93	4.96	9.96	13.6
9	201.3	3.94	4.97	9.97	13.8
10	200.8	3.92	4.96	9.95	13.9
Average	201.05	3.92	4.96	9.95	13.59
Minimum	200.1	3.91	4.96	9.95	12.7
Maximum	202.3	3.94	4.97	9.97	14

4.6.2.3 Weight variation, thickness, diameter and hardness of 600 mg round tablets:

Table 4.18: IPQC for 600 mg round tablet

Sr. No	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (kp)
1	602.3	5.49	10.97	25.3
2	601.3	5.48	10.98	24.7
3	600.3	5.49	10.97	24.7
4	601.5	5.49	10.98	25.8
5	601.2	5.48	10.97	25.4
6	602.3	5.49	10.98	24.6
7	600.3	5.48	10.97	25.4
8	601.3	5.49	10.98	26.3

9	601.4	5.48	10.97	24.4
10	600.4	5.49	10.98	25.3
Average	601.23	5.48	10.97	25.19
Minimum	600.3	5.48	10.97	24.4
Maximum	602.3	5.49	10.98	26.3

4.6.2.4 Weight variation, thickness width, length and hardness of 600 mg oval tablets:

Table 4.19: IPQC for 600 mg oval tablet

Sr. No	Weight (mg)	Thickness (mm)	Width (mm)	Length (mm)	Hardness (kp)
1	602.1	4.94	7.45	16.31	23.8
2	601.3	4.95	7.43	16.32	24.5
3	602.6	4.94	7.44	16.31	23.7
4	601.2	4.95	7.45	16.32	24.1
5	600.1	4.95	7.44	16.32	23.9
6	600.1	4.94	7.45	16.34	24.1
7	600.3	4.95	7.45	16.32	24.2
8	601.2	4.95	7.46	16.31	23.8
9	601.2	4.95	7.45	16.32	24.1
10	600.2	4.95	7.44	16.31	25.2
Average	601.03	4.94	7.44	16.31	24.14
Minimum	600.1	4.94	7.43	16.31	23.7
Maximum	602.6	4.95	7.46	16.34	25.2

Result and discussion: From the above mentioned data for composition of core tablets, it was concluded that core tablet batches were within the acceptable limits of weight variation, thickness, width, length and hardness.

4.6.2.5 % Friability for different shape tablets:

Table 4.20: % Friability with different shape tablets

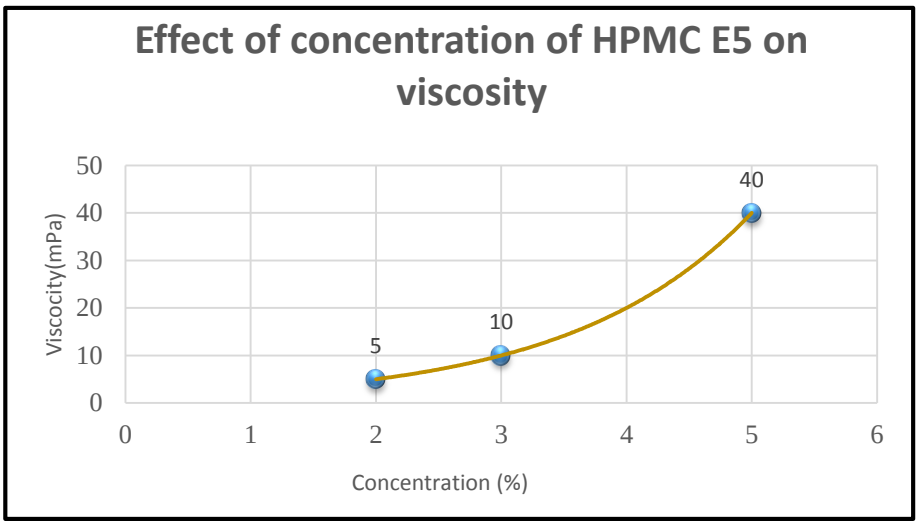
Shape	% Friability			
	For 100 counts	For 300 counts	For 500 counts	Observation
Round 200	0.1	0.7	0.8	Pass
Oval 200	0.15	0.2	0.9	Pass
Round 600	0.2	0.43	0.71	Pass
Oval 600	0.1	0.2	0.52	Pass

Result and discussion: From the above data it was concluded that the preliminary batches were acceptable as per friability test.

4.7 SELECTION OF CONCENTRATION OF HPMC E5 FOR COATING

- HPMC is well known to be a frequently used and simple coating material. For coating purposes HPMC with low viscosity is used, between 2% to 20% depending on the viscosity. The required viscosity of a HPMC aqueous coating solution is commonly less than 100mPa.
- 2%, 3% and 5% concentration of HPMC E5 solution was prepared. The viscosity of the solution was measured and coating was carried out on core tablets.

Figure 4.8: Effect of concentration of HPMC E5 on viscosity



Result and discussion:

The goal was to make coating formulation that is as simple as possible, i.e. a coating solution without any extra excipients. 2% concentration had too low viscosity. 3 % concentration and 5% concentration of coating solution formed thin coat layer on the tablet and did not had much difference during formation of film on tablets. So 3% concentration was optimized and used for further trials.

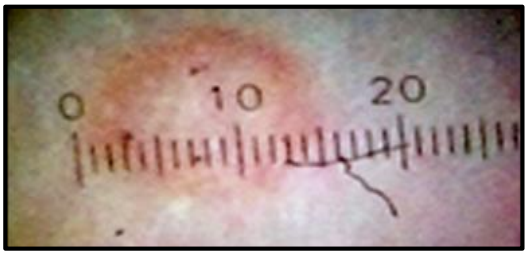
4.8 DROPLET SIZE DETERMINATION

Procedure

- The coating solution prepared was sprayed on rectangular piece of paper. From the spray cone obtained, square piece was cut from four sides and from center and observed under the optical microscope under 4x magnification.

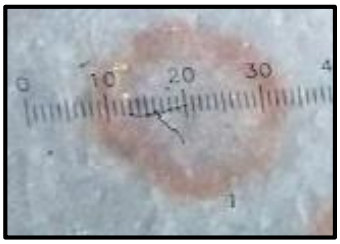
  Factor, 1 division = 26.6µ

  Magnification: 4x

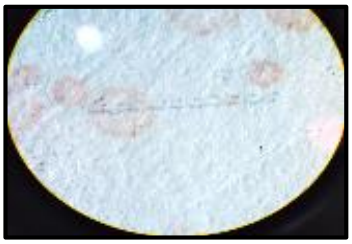


Droplet size: 399.1µ

Droplet size: 505.4 µ



Droplet size: 638.1 µ



Droplet size: 851.2 µ

Droplet size: 1.223 µ

Discussion:

- Smaller droplet size creates spray drying on tablet surface.
- Larger droplet size generates comparatively low coating uniformity.

- Hence optimum range is necessary for coating uniformity.
- Here optimum range is 600 – 1000 µ.

4.9 PREPARATION OF COATING SOLUTION

4.9.1 Composition of coating solution for 200 mg round and oval tablet:

Table 4.21: Coating Solution for 200 mg round and oval tablet

Material Used	mg/tablet	Qty for 4000 tablet	Overages (10%)
Core tablets	200	800 g	800 g
11AD (API)	3	12 g	13.2 g
HPMC E 5	5	20 g	22 g
Water	q.s	608 g	668.8 g
Total	208	640 g	704 g
Total solid content to be sprayed		8 mg	
% of solid in coating solution		5% w/w	
% Weight gain		4% w/w	

4.9.2 Composition of coating solution for 600 mg round and oval tablet:

Table 4.22: Coating Solution for 600 mg round and oval Tablet

Material Used	mg/tablet	Qty for 1334 tablet	Overages (10%)
Core tablets	600	800 g	800 g
11AD (API)	3	4 g	4.4 g
HPMC E 5	5	6.67 g	7.33 g
Water	q.s	202.66 g	222.92 g
Total	608	213.33 g	234.65 g
Total solid content to be sprayed		8 mg	
% of solid in coating solution		5% w/w	
% Weight gain		1.33% w/w	

4.9.3 Method for Preparation of coating solution:

- The weighed amount of HPMC powder was first dispersed into a partial amount (half to one-third of the total amount used) of hot water preferably over 70° C to prevent lumping and then cold water was added with constant stirring using overhead stirrer.
- A clear solution was obtained after cooling.
- The weighed amount of 11AD was then added to the coating solution and stirred constantly.

4.9.4 API coating of solution to core tablets

- The tablet cores were pre warmed in a coating pan for about 10 to 15 minutes. 30 warmed tablets were weighed.
- Drying of the tablets was continued until the moisture and tablet weight became constant. Pan speed was chosen on the basis of proper tumbling of tablets in the coater.
- 30 tablets were weighed at interval of 10 minutes (and the weight recorded) until the final weight gain of tablet was achieved. Curing of coated tablets was done until the tablet weight became constant.

4.10 PRELIMINARY TRIALS FOR COATING

Rationale for conducting Preliminary Trials:

➨ The preliminary trials were conducted in order to optimize the pan load for different shape and weight of tablets and to correlate the effect of spray rate and pan rpm on the content uniformity and coating process efficiency of tablets.

4.10.1 Constant parameters during coating:

Table 4.23: Parameters fixed during coating process

Parameters	Values
Inlet Temperature (ºC)	**65º**
Outlet temperature (ºC)	**50º**
Bed temperature (ºC)	**38-40º**
Atomization (cfm)	**1.2**
Fan (kg/cm^2)	**1.0**
Gun to Bed distance (cm)	**9.5**
Nozzle size of Gun (mm)	**1**

4.10.2 Preliminary trials for coating on core tablets:

Table 4.24: Preliminary trials for 200 mg round and oval tablets

Parameters	Round Shape		Oval Shape	
Weight of Core tablet	**200 mg**		**200 mg**	
Spray Rate	3-4g/min	3-4g/min	3-4g/min	3-4g/min
Pan Rpm	16	16	16	16
Pan load	600	800	600	800
Result				
% RSD	**7.2**	**4**	**8.4**	**5.9**
AV	**17**	**9.5**	**21.2**	**14.2**
%CPE	**81.2**	**94.1**	**75.7**	**81.2**

Table 4.25: Preliminary trials for 600 mg round and oval tablets

Parameters	**Round Shape**		**Oval Shape**	
Weight of Core tablet	**600 mg**		**600 mg**	
Spray Rate	3-4g/min	3-4g/min	3-4g/min	3-4g/min
Pan Rpm	12	12	12	12
Pan load	600	800	600	800
Result				
% RSD	**8.6**	**4.6**	**7.5**	**4.6**
AV	**20.4**	**11.8**	**19.5**	**10.9**
%CPE	**81.2**	**92.1**	**72.8**	**84.2**

Conclusion and Discussion

- From all the above trials it can be concluded that 800g pan load is preferred over 600g pan load as the value of % RSD, % CPE and the acceptance value of 800g pan load shows better results and within the range. Hence pan load of 800g will be taken to carry out further trials to optimize the spray rate and pan rpm.
- 3^2 full factorial design was selected as the design of experiment with independent variables as:
    1. Spray rate
    2. Pan rpm
- Here, 3^2 full factorial design was selected to study the effect of spray rate and pan rpm on % RSD of assay and % CPE.
- In 3^2 full factorial design, 3 levels are usually referred to as low, intermediate and high levels represented as (-1, 0, +1).
- This is the simplest three combinations design with maximum possible runs as compared to other response surface methodology designs.

- In this design, two factors are evaluated, each at three levels and experimental trials were carried out at all nine possible combinations.

4.11 FORMULATION DESIGN AS PER 3^2 FULL FACTORIAL EXPERIMENTAL DESIGNS

4.11.1 Independent variables and their coded values investigated for 200 mg round tablets using 3^2 full factorial design

Table 4.26: Independent variable and their coded value for 200 mg round tablets

Levels (coded value)	**Independent Variables**	
	Spray Rate (g/min)	**Pan Speed (Rpm)**
-1	3.5	16
0	4.5	18
+1	5.5	20
Dependent Variables	**% RSD***	
	% CPE*	

* % RSD = % Relative Standard Deviation

* % CPE = % Coating Process Efficiency

Table 4.27: Optimization of 200mg round tablets using 3^2 full factorial experimental designs

Batch no	**Run**	**Coded values**		**Responses**	
		Spray Rate (g/min)	**Pan speed (rpm)**	**% RSD**	**% CPE**
A1	1	-1	-1	4	94.2
A2	2	-1	0	3.4	97.5
A3	3	-1	+1	2.9	97.6
A4	4	0	-1	4.6	92.6
A5	5	0	0	3.7	96.1
A6	6	0	+1	3.1	98.3
A7	7	+1	-1	4.9	90.5

A8	8	+1	0	3.9	94.3
A9	9	+1	+1	4.1	94.6

4.11.1.1 ***Results and discussion:***

Table 4.28: Acceptance value and % Assay of 200 mg round tablets

Batch	***A1***	***A2***	***A3***	***A4***	***A5***	***A6***	***A7***	***A8***	***A9***
% Assay	***97.9***	***99.0***	***94.9***	***100.1***	***97.4***	***99.1***	***97.4***	***99.0***	***98.4***
AV	***10.4***	***8.1***	***10.2***	***11.2***	***9.8***	***9.6***	***14.3***	***9.3***	***10.8***

Figure 4.9: Graph for acceptance value of DoE batches of 200 mg round tablets

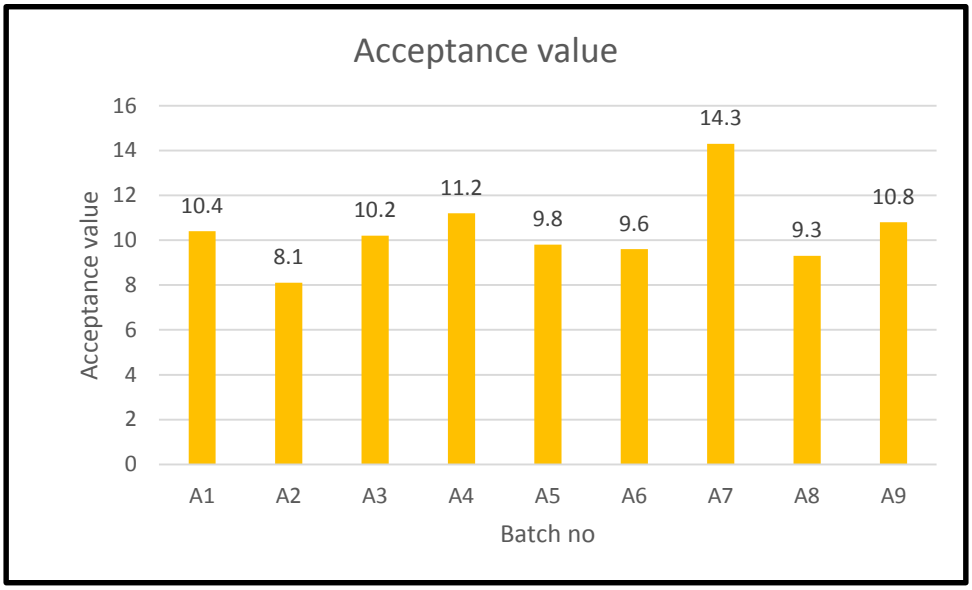


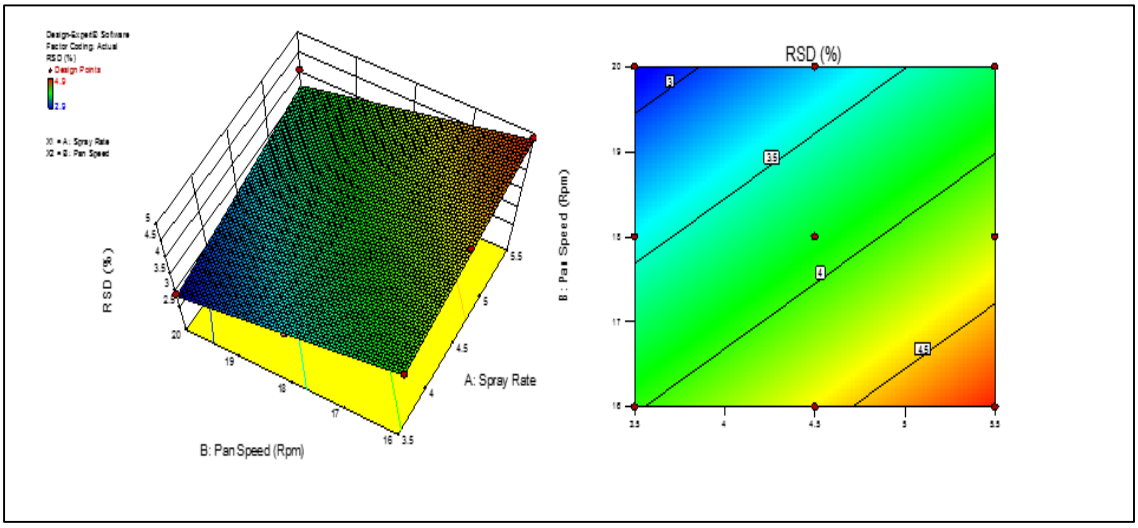
Table 4.29: Result of ANOVA for % RSD of 200 mg round tablets

Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**Df**	**Mean Square**	**F Value**	**p-value Prob> F**	
Model	3.05	2	1.53	23.55	0.0014	Significant

A-Spray Rate	*1.13*	*1*	*1.13*	*17.38*	*0.0059*	
B-Pan Speed	*1.93*	*1*	*1.93*	*29.73*	*0.0016*	
Residual	0.39	6	0.065			
Cor Total	3.44	8				

Predicted model	Linear
Equation	RSD = +3.84+0.43*A-0.57*B
R^2 value	0.887
Predicted R^2 value	0.7267
Adjusted R^2 value	0.8494

Figure 4.10: Response surface plot and contour plot for % RSD of round 200 mg tablet



Discussion:

Here, linear model was found to be significant. The R^2 value of 0.887 indicated good fit of model. From probability value p = 0.0059, it was concluded that pan speed was major factor which affect % RSD. The range of % RSD was found to be between 2.9 to 4.9 which was witihn the acceptable limits of % RSD.

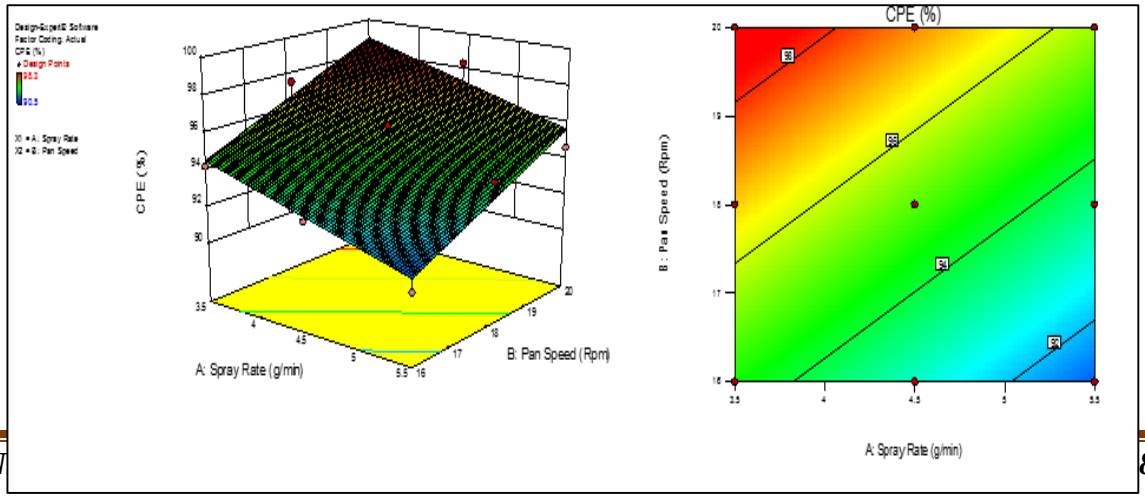
Highest spray rate (5.5 g/min) and lowest pan speed (16 rpm) showed highest value of % RSD among all the batches. As the pan rpm increased, % RSD decreased, this is because tablets get

more chance to pass through the spray zone cycle and so the tablet gets more even and uniform distribution of coat. From the data of % RSD, it was observed that increase in the pan speed led to decrease in the value of % RSD. From data of batch A1, A4 and A7 it was observed that increase in spray rate showed increase in the value of % RSD while keeping same pan speed.

Table 4.30: Result of ANOVA for % CPE of 200 round mg tablet

Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**Df**	**Mean Square**	**F Value**	**p-value Prob> F**	
Model	45.37	2	22.69	19.50	0.0024	Significant
A-Spray Rate	*16.33*	*1*	*16.33*	*14.04*	*0.0095*	
B-Pan Speed	*29.04*	*1*	*29.04*	*24.96*	*0.0025*	
Residual	6.98	6	1.16			
Cor Total	52.36	8				
Predicted model		Linear				
Equation		% CPE = 95.08 - 1.65*A + 2.20 * B				
R^2 value		0.8667				
Predicted R^2 value		0.6701				
Adjusted R^2 value		0.8222				

Figure 4.11: Response surface plot and contour plot for % CPE of 200 mg round tablets



Discussion:

Linear model was found significant here. R^2 value of 0.8667 indicated good correlation between factors and responses. From probability value p = 0.0025, it was concluded that pan speed was major factor which affect % CPE.

Coating process efficiency for coated tablet varied from 90.5 - 98.3 %. Highest spray rate (5.5g/min) and lowest pan speed (16 rpm) led to lowest coating process efficiency of 90.5. Increase in pan speed from -1 to +1 level showed increase in the value of % CPE.

Table 4.31: Evaluation for 200 mg round tablets

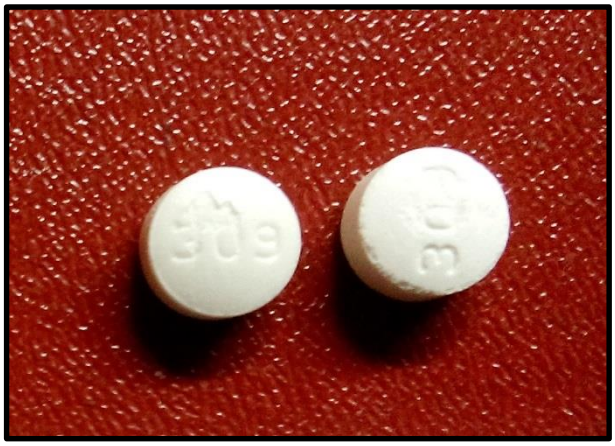
	For 200 mg round tablets						
Batch no	**Time (min)**	**Thickness (mm)**		**Diameter (mm)**		**Defects**	**Defects Ranking**
		Uncoated	**Coated**	**Uncoated**	**Coated**		
A1	180	3.96 ± 0.004	4.06 ± 0.009	7.48 ± 0.005	7.6 ± 0.006	-	0
A2	180	3.96 ± 0.004	4.06 ± 0.009	7.48 ± 0.005	7.6 ± 0.006	-	0
A3	180	3.97 ± 0.004	4.06 ± 0.009	7.48 ± 0.005	7.59 ± 0.006	Roughness	3
A4	160	3.96 ± 0.004	4.06 ± 0.009	7.49 ± 0.005	7.6 ± 0.006	-	0
A5	160	3.96 ± 0.004	4.06 ± 0.009	7.48 ± 0.005	7.61 ± 0.006	-	0
A6	160	3.97 ± 0.004	4.06 ± 0.009	7.49 ± 0.005	7.6 ± 0.006	-	0
A7	130	3.96 ± 0.004	4.06 ± 0.009	7.48 ± 0.005	7.59 ± 0.006	-	0
A8	130	3.96 ± 0.004	4.06 ± 0.009	7.49 ± 0.005	7.59 ± 0.006	Sticking of tablets	1
A9	130	3.96 ± 0.004	4.06 ± 0.009	7.49 ± 0.005	7.6 ± 0.006	-	0

Tablet Ranking: Ranking of tablet defect was done by visual inspection of 100 tablets which were selected randomly from the batch. The ranking of defected tablets are given in the table 4.32.

Table 4.32: Ranking of tablet defects

No. of defective tablets	Ranking	Acceptability
0	0	Highly acceptable
<10	1	Acceptable
10 – 20	2	Reasonably acceptable
>20	3	Not acceptable

Figure 4.12 Tablet defect of 200 mg round tablet



Sticking of tablet

Result and Discussion for factorial design of round 200 mg tablet:

- Linear model was found significant for both % RSD and % CPE. It indicated that medium and high pan speed shows better CPE and decreased value of % RSD as compared to lower rpm.
- Increasing the spray rate increases the value of % RSD of assay.

Optimized batch: Batch A6 having Pan Speed of 20 rpm and Spray rate of 4.5g/min is the optimized batch as the % RSD of this batch is 3.1 g/min and has coating process efficiency of 98.3 rpm with no visible tablet defects. Batch A3 had lowest value of %

RSD of 2.9, but the acceptance value of batch A3 was 10.2 and the coating time was 180 min while for batch A6 the acceptance value was 9.6 and the coating time was 160 min. Hence considering the data of % RSD, acceptance value, coating time and visual defects batch A6 was optimized.

4.11.2 Check point batch analysis for 200 mg round tablet

4.11.2.1 Data of check point batch:

Figure 4.13: Results of check point batch analysis for round 200 mg tablet

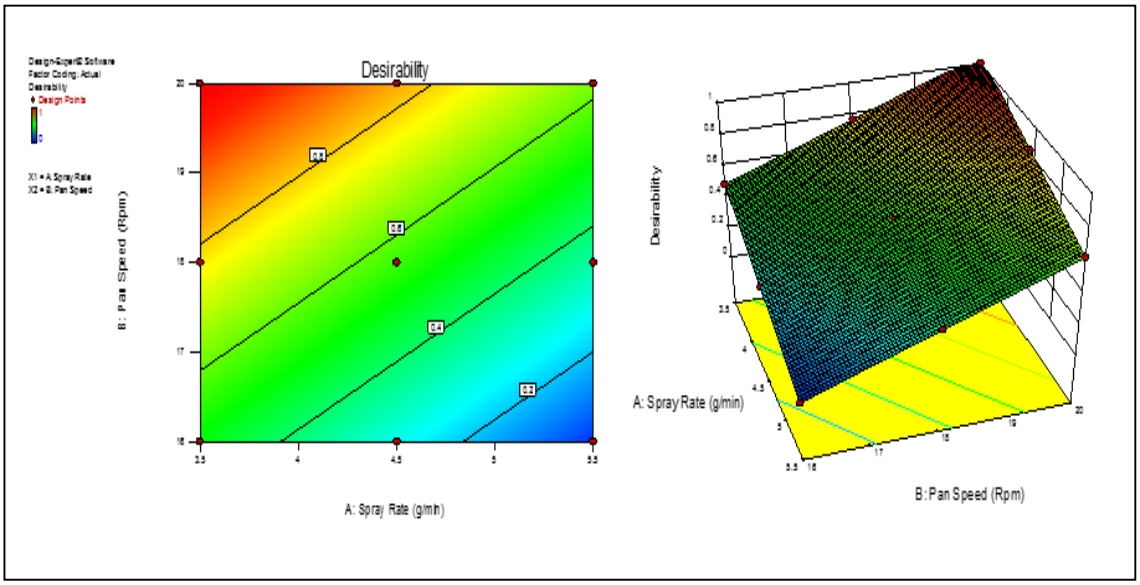


Table 4.33: Comparison between experimental and predicted values for check point batch for 200 mg round tablets

Spray rate = 4 g/min	Pan Speed = 17 rpm	
Parameters	**% RSD**	**% CPE**
Predicted	3.89	94.98
Experimental	4.1	95.4
Calculated	0.121	0.113
Tabulated	6.313	6.313

Discussion:

The models developed nearly same values as that of experimental values. So, this model can be said to be **validated** model for the given full factorial design.

4.11.3 Independent variables and their coded values investigated for 200mg Oval tablets using 3^2 full factorial design:

Table 4.34: Independent variable and their coded value for 200mg Oval tablets

Levels (coded value)	**Independent Variables**	
	Spray Rate (g/min)	**Pan Speed (Rpm)**
-1	3.5	16
0	4.5	18
+1	5.5	20
Dependent Variables	**% RSD***	
	% CPE*	

Table 4.35: Optimization design of 200 mg oval tablet using 3^2 full factorial experimental designs

Batches	**Run**	**Coded values**		**Responses**	
		Spray rate (g/min)	**Pan speed (rpm)**	**% RSD**	**% CPE**
B1	1	-1	-1	5.9	81.6
B2	2	-1	0	5.1	87.1
B3	3	-1	1	4	91.8
B4	4	0	-1	5.3	85.9
B5	5	0	0	4.9	89.5
B6	6	0	1	3.5	96.1
B7	7	1	-1	4.7	90.9
B8	8	1	0	3.1	97.5

B9	9	1	1	3.7	94.4

4.11.3.1 Results and discussion:

Table 4.36: % Assay and Acceptance value of 200 mg oval tablets

Batch	*B1*	*B2*	*B3*	*B4*	*B5*	*B6*	*B7*	*B8*	*B9*
% Assay	*97.2*	*101.5*	*97.9*	*98.1*	*97.7*	*99.9*	*95.5*	*99.1*	*100.2*
Av	*11.4*	*12.3*	*10.0*	*12.2*	*12.2*	*10.8*	*11.2*	*9.6*	*10.8*

Figure 4.14: Graph for acceptance value of DoE batches of 200 mg Oval tablets

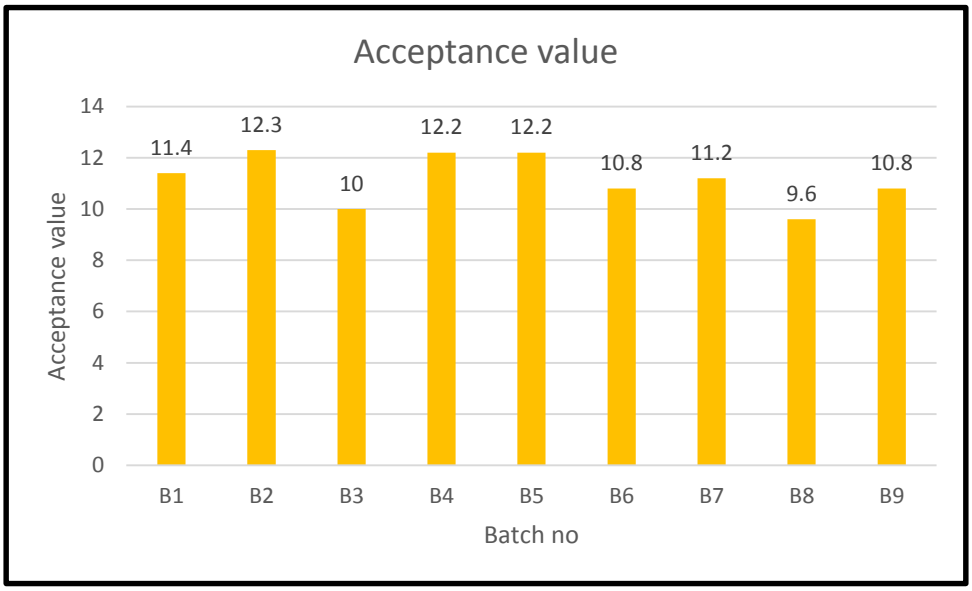
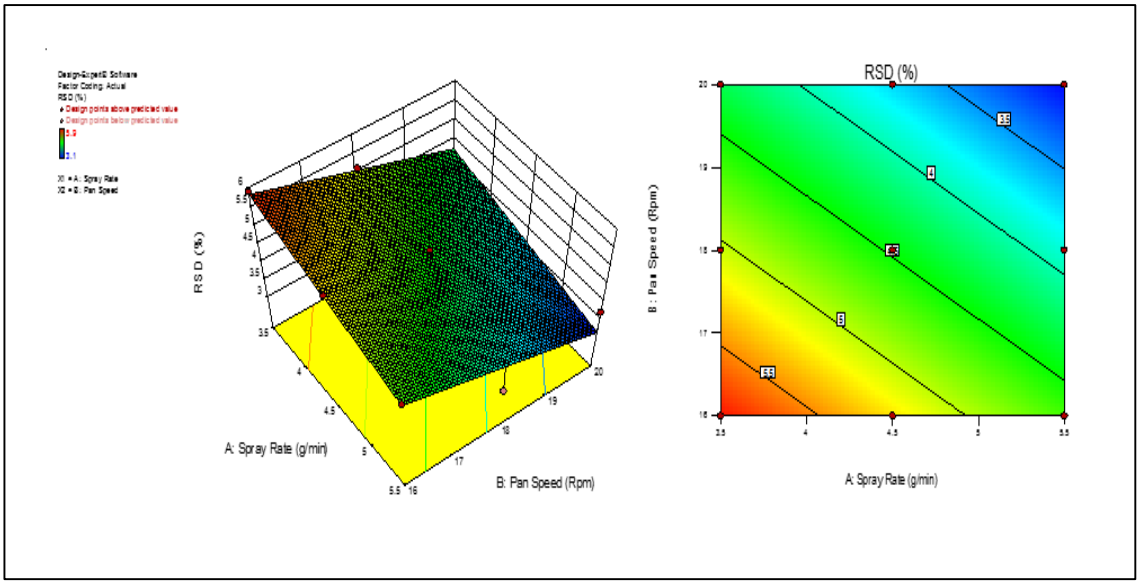


Table 4.37: Result of ANOVA for % RSD of Oval 200mg tablets

Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**Df**	**Mean Square**	**F Value**	**p-value Prob> F**	
Model	5.72	2	2.86	13.45	0.0061	significant
A-Spray Rate	2.04	1	2.04	9.60	0.0212	
B-Pan Speed	3.68	1	3.68	17.30	0.0059	

Residual	1.28	6	0.21			
Cor Total	7.00	8				
Predicted model	Linear					
Equation	% RSD = +4.47 – 0.58*A – 0.78*B					
R^2 value	0.8176					
Predicted R^2 value	0.5853					
Adjusted R^2 value	0.7568					

Figure 4.15: Response surface plot and contour plot for % RSD of 200 mg oval tablets



Discussion:

Linear model was found to be significant. The R^2 value of 0.8176 indicated good fit of model. From probability value p = 0.0059, it was concluded that pan speed was major factor which affect % RSD. The range of % RSD was found to be between 3.1-5.9 g/min.

Low spray rate and low pan speed had highest borderline value of % RSD. Low pan speed combination with high, medium and low values of spray rate showed higher values of %

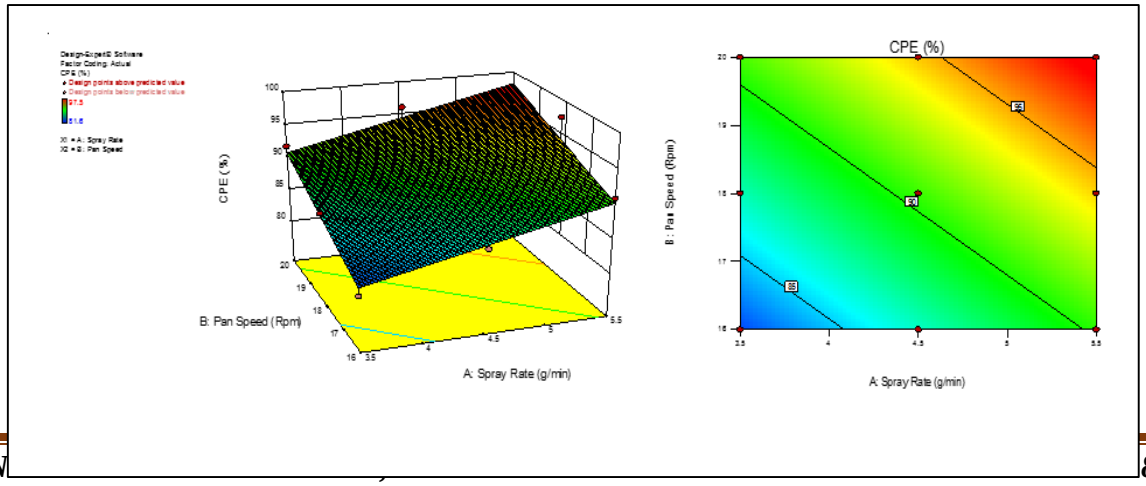
RSD. A combination of lowest pan speed and lowest spray rate showed highest value of 5.9 % RSD.

Table 4.38: Result of ANOVA for % CPE of 200mg oval tablets

Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob> F**	
Model	178.08	2	89.04	16.56	0.0036	Significant
A-Spray Rate	82.88	1	82.88	15.42	0.0077	
B-Pan Speed	95.20	1	95.20	17.71	0.0056	
Residual	32.26	6	5.38			
Cor Total	210.34	8				

Predicted model	Linear
Equation	% CPE = 90.53 + 3.72*A + 3.98*B
R^2 value	0.8466
Predicted R^2 value	0.5985
Adjusted R^2 value	0.7955

Figure 4.16: Response surface plot and contour plot for % CPE of 200 mg oval tablets



Discussion: Linear model was found to be significant. The R^2value indicated good fit of model. From probability value of p = 0.0056 it was found that pan speed was major factor affecting % CPE. The range of % CPE was 81.6 – 97.5 %.From the above results it was observed that lowest pan speed with low, medium and high level of spray rate led to wide range of % CPE from 81.6 to 90.9. As the value of pan speed increased the value of % CPE increased.

Table 4.39: Evaluation of 200 mg oval tablets.

		For 200 mg oval tablets							
Batch No	**Time (min)**	**Thickness (mm)**		**Length (mm)**		**Width (mm)**		**Defects**	**Defect ranking**
		Uncoated	**Coated**	**Uncoated**	**Coated**	**Uncoated**	**Coated**		
B1	180	3.91 ± 0.02	4.05 ± 0.02	9.95 ± 0.01	10.07 ± 0.02	4.96 ± 0.03	5.06 ± 0.03	-	0
B2	180	3.92 ± 0.03	4.06 ± 0.03	9.96 ± 0.01	10.05 ± 0.02	4.97 ± 0.02	5.07 ± 0.02	-	0
B3	180	3.92 ± 0.03	4.06 ± 0.02	9.96 ± 0.03	10.06 ± 0.03	4.96 ± 0.02	5.07 ± 0.02	Surface roughness	1
B4	160	3.91 ± 0.02	4.06 ± 0.02	9.96 ± 0.04	10.07 ± 0.03	4.96 ± 0.03	5.07 ± 0.02	-	0
B5	160	3.91 ± 0.02	4.05 ± 0.02	9.95 ± 0.02	10.07 ± 0.03	4.96 ± 0.01	5.07 ± 0.02	-	0
B6	160	3.92 ± 0.03	4.06 ± 0.01	9.96 ± 0.02	10.07 ± 0.03	4.97 ± 0.02	5.06 ± 0.03	-	0
B7	130	3.91 ± 0.02	4.05 ± 0.02	9.95 ± 0.03	10.06 ± 0.02	4.96 ± 0.03	5.07 ± 0.02	Sticking of tablets	2
B8	130	3.92 ± 0.03	4.05 ± 0.03	9.96 ± 0.01	10.07 ± 0.03	4.97 ± 0.02	5.07 ± 0.02	-	0
B9	130	3.92 ± 0.03	4.06 ± 0.02	9.96 ± 0.03	10.07 ± 0.03	4.96 ± 0.03	5.06 ± 0.03	Edge breaking	2

Figure 4.17: Tablet defects for 200 mg oval tablets

Sticking of tablets **Edge breaking**

Discussion:

Here the linear model was found to be significant. From the above results it was concluded that lowest pan speed led to highest unacceptable value of % RSD with decline in % CPE from 81.5 to 90.9. While increase in the pan speed from 16 to 20 lead to increase in the value of % RSD indicating that pan rpm has significant effect on % RSD and % CPE. Though increase in pan speed led to increase in the value of % RSD, Edge breaking was the major tablet defect observed at highest speed of 20 rpm. Hence selection of appropriate batch was critical.

It was observed that when pan rpm increased, % RSD got decreased but % CPE showed major variation moreover, defects were observed at high rpm so it can be concluded that oval 200 is more critical to coat as compared to 200 mg round tablets.

Optimized batch: B8 batch with spray rate of 5.5g/min and pan speed of 18 had the lowest % RSD of 3.1 and coating process efficiency of 97.5% with no visible signs of tablet defects.

4.11.4 Check point batch analysis for 200 mg oval tablets

4.11.4.1 Data for check point batch:

Figure 4.18: Results of check point batch analysis for 200 mg oval tablets

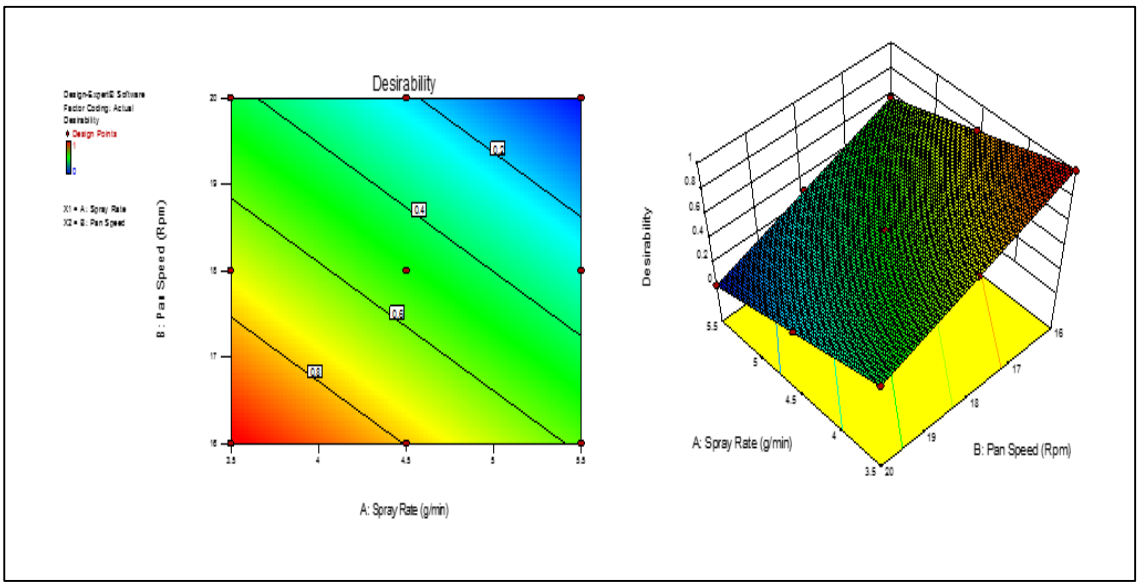


Table 4.40: Comparison between experimental and predicted values for check point batch for 200 mg oval tablets

Spray rate = 5 g/min	Pan Speed =19 rpm

Parameters	**% RSD**	**% CPE**
Predicted	3.67	95.014
Experimental	3.98	96.2
Calculated	0.114	0.149
Tabulated	6.313	6.313

Discussion:

The models developed nearly same values as that of experimental values. So, this model can be said to be **validated** model for the given full factorial design.

4.11.5 Independent variables and their coded values investigated for 600 mg round tablets using 3^2 full factorial design:

Table 4.41: Independent variable and their coded value for 600 mg round tablets

Levels (coded value)	Independent Variables	
	Spray Rate (g/min)	Pan Speed (Rpm)
-1	3.5	12
0	4.5	14
+1	5.5	16
Dependent Variables	% RSD	
	% CPE	

Table 4.42: Optimization design of 600 mg round tablets using 3^2 full factorial experimental designs

Batches	Run	Coded values		Responses	
		Spray rate (g/min)	Pan speed (rpm)	% RSD	%CPE
C1	1	-1	-1	4.6	92.9
C2	2	-1	0	3.7	94.3
C3	3	-1	+1	3.2	96.7
C4	4	0	-1	5.1	92.1
C5	5	0	0	4.3	93
C6	6	0	+1	3.5	94.1
C7	7	+1	-1	6.3	89.4
C8	8	+1	0	6.1	90.6
C9	9	+1	+1	5.1	91.2

4.11.5.1 Result and discussion

Table 4.43: % Assay and Acceptance value of 600 mg round tablets

Batch	*C1*	*C2*	*C3*	*C4*	*C5*	*C6*	*C7*	*C8*	*C9*
% Assay	*100.7*	*97.4*	*100.2*	*102.3*	*99.7*	*98.2*	*101.0*	*99.6*	*97.8*
Av	*11.1*	*9.8*	*7.7*	*13.4*	*10.3*	*10.5*	*15.8*	*14.6*	*12.1*

Figure 4.19: Graph for acceptance value of DoE batches of 600 mg round tablets

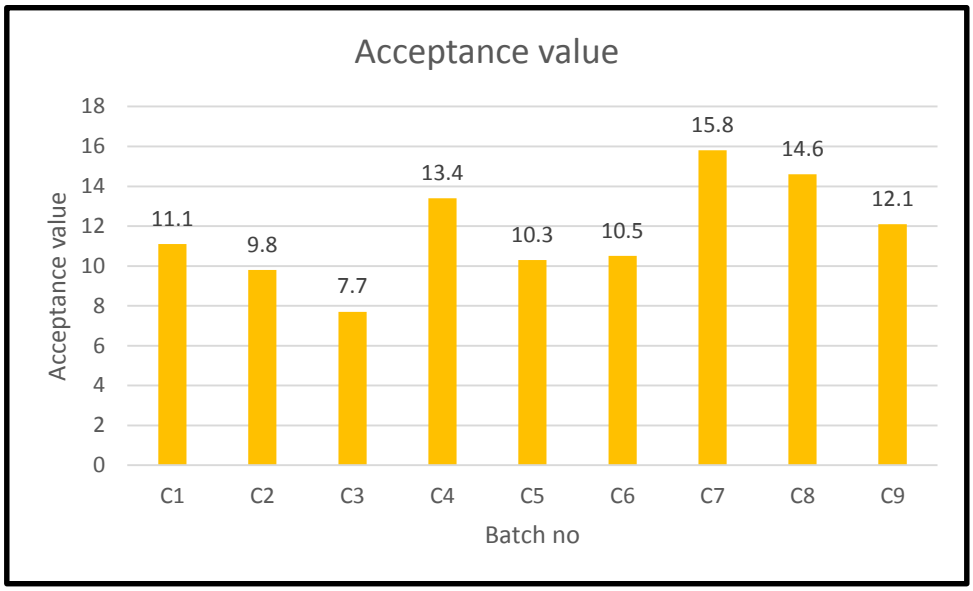
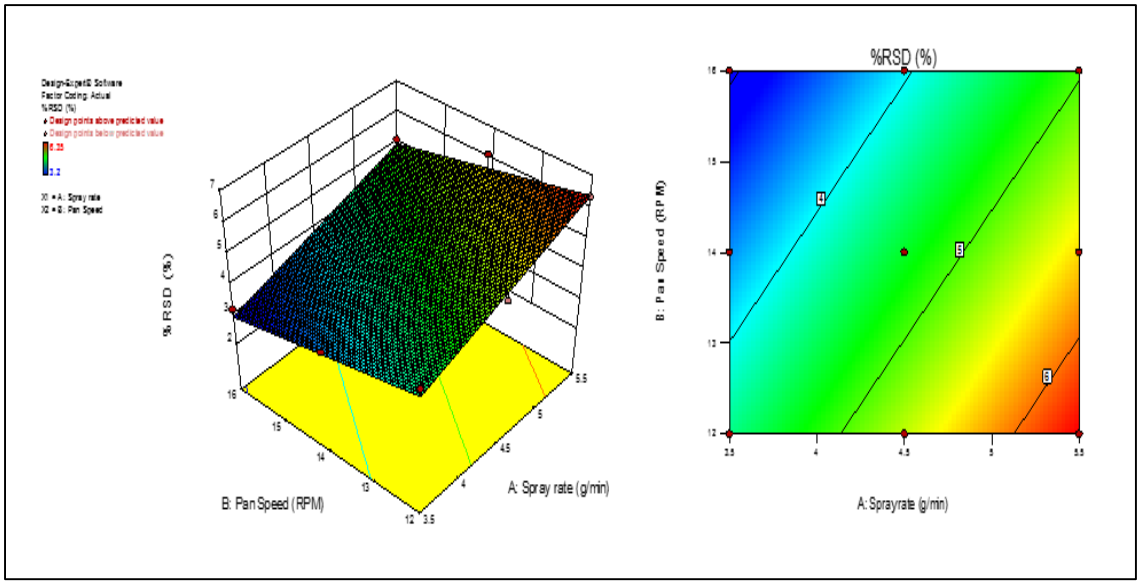


Table 4.44: Result of ANOVA for % RSD of 600 mg round tablets

Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob> F**	
Model	9.11	2	4.56	37.03	0.0004	Significant
A-Spray rate	6.10	1	6.10	49.59	0.0004	
B-Pan Speed	3.01	1	3.01	24.47	0.0026	
Residual	0.74	6	0.12			
Cor Total	9.85	8				

Predicted model	Linear
Equation	% RSD = +4.66 + 1.01 *A – 0.71* B
R^2 value	0.9251
Predicted R^2 value	0.8458
Adjusted R^2 value	0.9001

Figure 4.20: Response surface plot and contour plot for % RSD of 600 round mg tablet



Discussion:

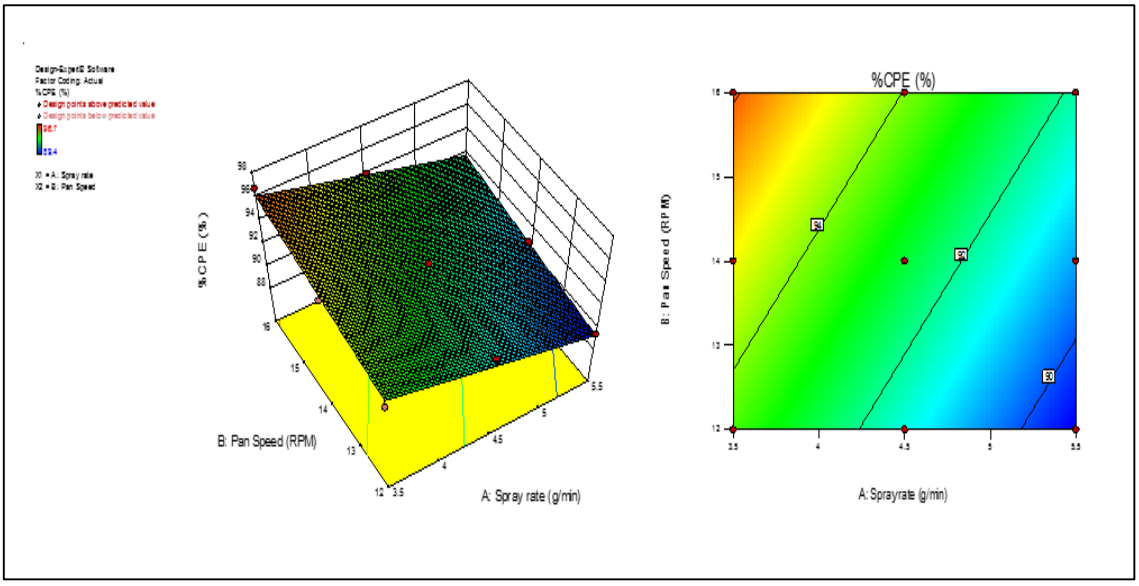
Linear model was found to be significant. The value of correlation coefficient (r^2) of equation was found to be 0.9251, indicating good fit. The data clearly indicated that dependent variables were strongly dependent on independent variables. The range of % RSD was found to be between 3.2 - 6.3 %.

Highest spray rate (5.5 g/min) and lowest pan speed (12 rpm) showed highest value of % RSD (6.3%) with sticking of tablets so the batch is considered to be unacceptable. Similarly batch C8 having % RSD of 6.1 is also considered as unacceptable batch as the value of % RSD is beyond the acceptable limits of % RSD.

Table 4.45: Result of ANOVA for % CPE of 600 mg round tablets

Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob> F**	
Model	36.51	2	18.25	53.38	0.0002	Significant
A-Spray rate	*26.88*	*1*	*26.88*	*78.61*	*0.0001*	
B-Pan Speed	*9.63*	*1*	*9.63*	*28.15*	*0.0018*	
Residual	2.05	6	0.34			
Cor Total	38.56	8				
Predicted model	Linear					
Equation	% CPE = 92.70 – 2.12* A + 1.27* B					
R^2 value	0.9468					
Predicted R^2 value	0.8572					
Adjusted R^2 value	0.9291					

Figure 4.21: Response surface plot and contour plot for % CPE of 600 mg round tablet

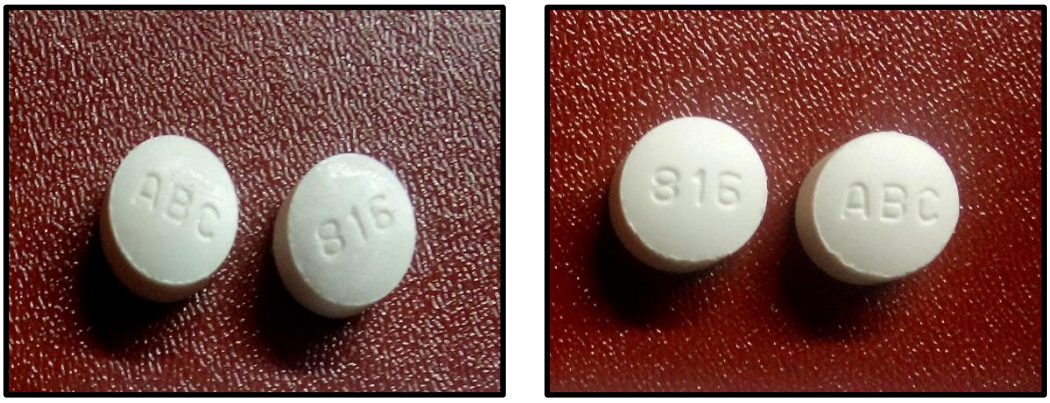


Discussion: Linear model was found to be significant. The R^2 value of equation was found to be 0.9468, indicating good fit. The range of % CPE was between 89.4-96.7 %. Highest spray rate and lowest pan speed showed lowest % CPE due to inefficient coating which was due to low speed of pan compared to the spray rate which led to nonuniform coating of tablets.

Table 4.46: Evaluation of 600 mg round tablets

	For 600 mg round tablets						
Batch No	**Time (min)**	**Thickness (mm)**		**Diameter (mm)**		**Defects**	**Defects Ranking**
		Uncoated	**Coated**	**Uncoated**	**Coated**		
C1	60	5.49 ± 0.003	5.64 ± 0.01	10.98 ± 0.005	11.04 ± 0.05	-	0
C2	60	5.50 ± 0.003	5.64 ± 0.01	10.97 ± 0.005	11.05 ± 0.05	-	0
C3	60	5.49 ± 0.003	5.65 ± 0.01	10.98 ± 0.02	11.04 ± 0.02	-	0
C4	50	5.49 ± 0.003	5.62 ± 0.01	10.97 ± 0.03	11.04 ± 0.02	-	0
C5	50	5.49 ± 0.003	5.64 ± 0.01	10.98 ± 0.02	11.04 ± 0.03	-	0
C6	50	5.49 ± 0.003	5.63 ± 0.01	10.98 ± 0.02	11.04 ± 0.02	-	0
C7	40	5.49 ± 0.003	5.64 ± 0.01	10.98 ± 0.02	11.05 ± 0.01	Sticking of tablets	3
C8	40	5.49 ± 0.003	5.62 ± 0.01	10.97 ± 0.03	11.04 ± 0.02	-	0
C9	40	5.49 ± 0.003	5.64 ± 0.01	10.97 ± 0.03	11.05 ± 0.03	Edge breaking	1

Figure 4. 22 Tablet defects of 600 mg round tablets



Sticking of tablets **Edge breaking**

Discussion

Linear model was found to be significant. % RSD value decreases and % CPE value increases with increase in pan speed. In comparison to round 200 mg tablet, round 600 mg is having higher RSD value and lesser CPE values which showed that same shape and lower weight tablet, showed better coating uniformity.

The results obtained showed variation from acceptable to highly unacceptable range of value of % RSD and % CPE. This indicates that coating parameters needs to be carefully selected for coating round 600 mg tablets. Batch C7 and C8 is considered as failed batch because the value of % RSD exceeded the limit of % RSD (<6 %).

Optimized batch: Batch C3 having spray rate of 3.5g/min and pan speed of 16 is considered as optimized batch because low spray rate and medium pan speed gave highest value of % CPE 96.7% and lowest % RSD value of 3.2g/min.

4.11.6 Check point batch analysis for round 600 mg tablets

4.11.6.1 Data for checkpoint batch

Figure 4.23: Results of check point batch analysis for round 600 mg tablet

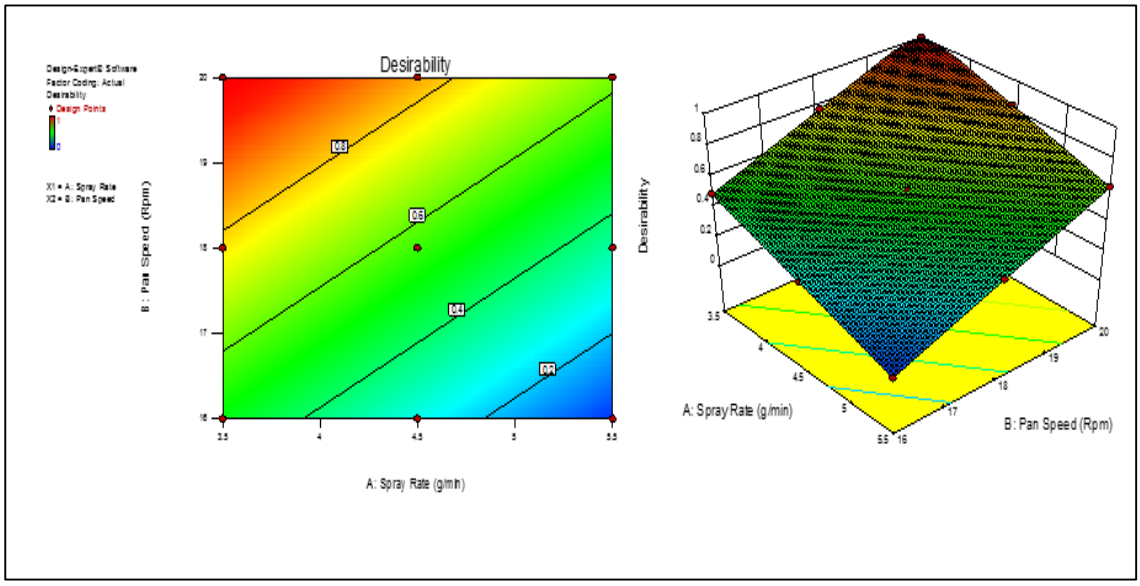


Table 4.47: Comparison between experimental and predicted values for check point of 600 mg round tablets

Spray rate = 4 g/min		Pan Speed = 14 rpm
Parameters	**% RSD**	**% CPE**
Predicted	**3.48**	**94.9558**
Experimental	**3.98**	**95.67**
Calculated	**0.0391**	**0.042**
Tabulated	**6.313**	**6.313**

Discussion:

The models developed nearly same values as that of experimental values. So, this model can be said to be **validated** model for the given full factorial design.

4.11.7 Independent variables and their coded values investigated for 600mg oval tablets using 3^2 full factorial design:

Table 4.48: Independent variable and their coded value for 600mg Oval tablets

Levels (coded value)	**Independent Variables**	
	Spray Rate (g/min)	**Pan Speed (Rpm)**
-1	3.5	12
0	4.5	14
+1	5.5	16
Dependent Variables	% RSD	
	% CPE	

Table 4.49: Optimization design of 600 mg oval tablets using 3^2 full factorial experimental designs

Batch no	**Run**	**Coded values**		**Responses**	
		Spray Rate (g/min)	**Pan speed (rpm)**	**%RSD**	**%CPE**
D1	1	-1	-1	4.6	84.7
D2	2	-1	0	4	84.3
D3	3	-1	+1	3.8	84
D4	4	0	-1	5.4	85.2
D5	5	0	0	4.6	84.9
D6	6	0	+1	4.7	84.6
D7	7	+1	-1	6.2	86
D8	8	+1	0	4.9	85.8
D9	9	+1	+1	5	85.4

4.11.7.1 Result and Discussion:

Table 4.50: % Assay and Acceptance value of 600 mg oval tablets

Batch	*D1*	*D2*	*D3*	*D4*	*D5*	*D6*	*D7*	*D8*	*D9*
% Assay	*100.1*	*99.3*	*98.9*	*97.5*	*97.1*	*97.5*	*99.6*	*98.4*	*101.5*
Av	*11.2*	*10.4*	*11.4*	*14.6*	*12.1*	*13.8*	*14.7*	*14.3*	*12.1*

Figure 4. 24: Graph for acceptance value of DoE batches of 600 mg oval tablets

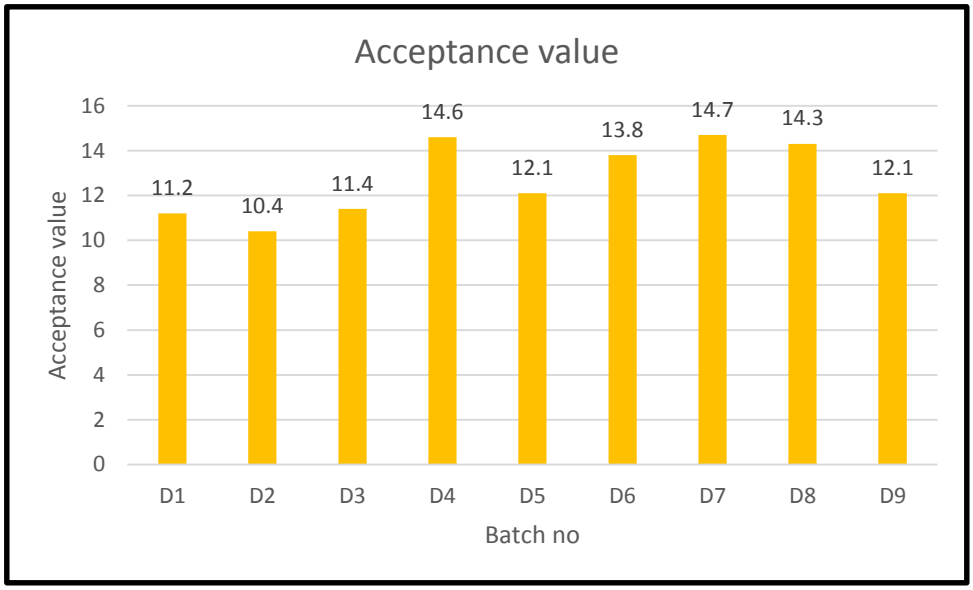


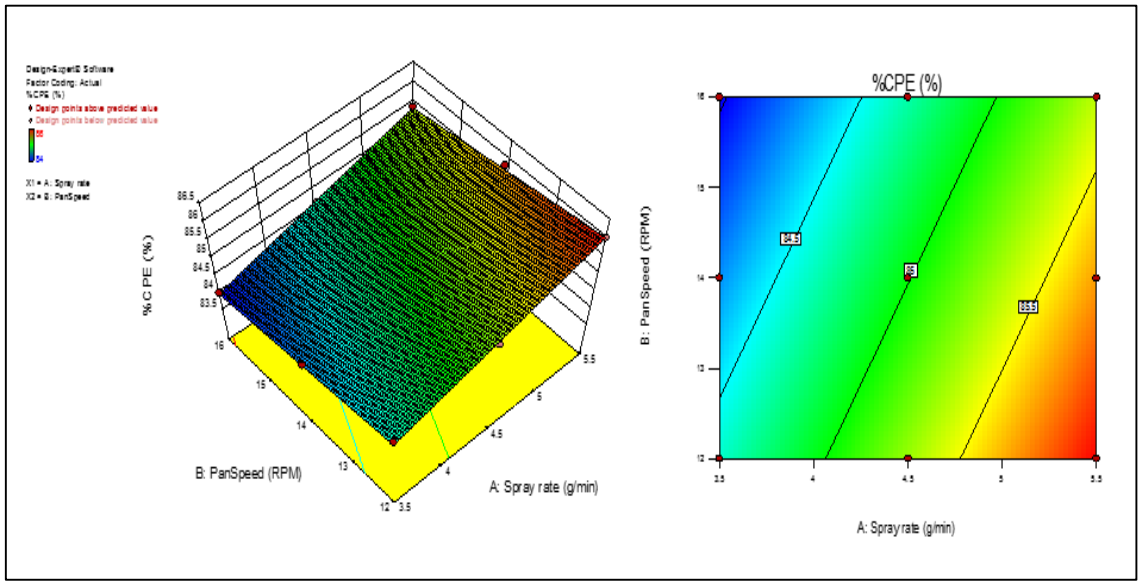
Table 4.51: Result of ANOVA for % RSD of Oval 600mg tablet

Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob> F**	
Model	3.50	2	1.75	17.39	0.0032	Significant
A-Spray rate	2.28	1	2.28	22.69	0.0031	
B-Pan Speed	1.22	1	1.22	12.08	0.0132	
Residual	0.60	6	0.10			

Cor Total	4.10	8				

Predicted model	Linear
Equation	% RSD = 4.80 + 0.62 * A – 0.45 * B
R^2 value	0.8528
Predicted R^2 value	0.6862
Adjusted R^2 value	0.8038

Figure 4.25: Response surface plot and contour plot for % RSD of Oval 600 mg tablet



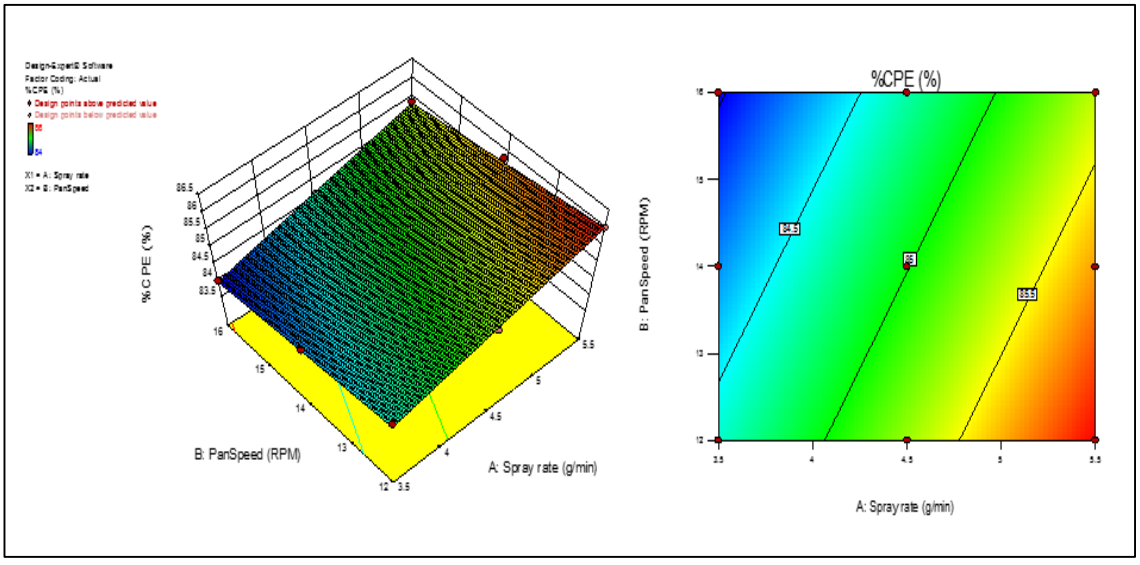
Discussion: Linear model was found to be significant. The R^2 value of 0.9868 indicated good fit of model. The values of % RSD is between 3.8 – 6.2%. Highest spray rate and lowest pan speed showed 6.2 % RSD which is outside the limit of % RSD (< 6).

Table 4.52: Result of ANOVA for % CPE of 600mg oval tablets

Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**Df**	**Mean Square**	**F Value**	**p-value Prob> F**	
Model	8.83	2	1.77	225	0.0182	Significant
A-Spray rate	4.00	1	4.00	373.55	<0.0001	
B-Pan Speed	0.000	1	0.000	76.45	<0.0001	
Residual	0.047	6				
Cor Total	3.59	8				

Predicted model	Linear
Linear	**% CPE = + 84.99 – 0.70*A – 0.32*B**
R^2 value	0.9868
Predicted R^2 value	0.9723
Adjusted R^2 value	0.9825

Figure 4.26: Response surface plot and contour plot for % CPE of Oval 600 mg tablet



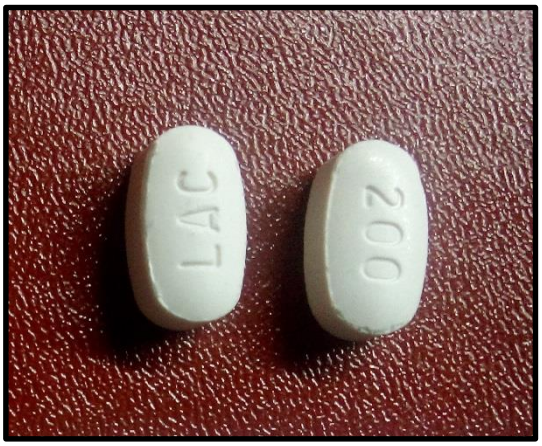
Discussion: Linear model was found to be significant. The R^2value indicated good fit of model. The range of % CPE was 84-86 %.The value of % CPE was found to be between 84-86 % which shows that coating process efficiency for 600 mg oval tablet is very less and narrow. Coating 600 mg oval tablet may prove to be critical.

Table 4.53: Evaluation of 600 mg oval tablets

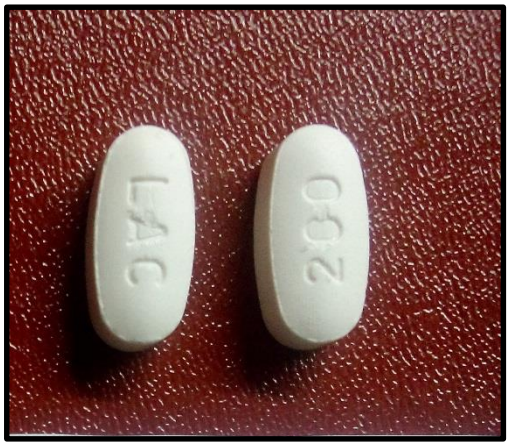
		For 600 mg oval tablets							
Batch no	**Time (min)**	**Thickness (mm)**		**Length (mm)**		**Width (mm)**		**Defects**	**Defects Ranking**
		Uncoated	**Coated**	**Uncoated**	**Coated**	**Uncoated**	**Coated**		
D1	60	4.94 ± 0.02	5.01 ± 0.02	16.31 ± 0.03	16.53 ± 0.03	7.45 ± 0.02	7.51 ± 0.02	-	0
D2	60	4.95 ± 0.02	5.01 ± 0.02	16.32 ± 0.03	16.53 ± 0.03	7.43 ± 0.03	7.52 ± 0.03	-	0
D3	60	4.94 ± 0.03	5.02 ± 0.03	16.32 ± 0.03	16.53 ± 0.03	7.44 ± 0.04	7.51 ± 0.04	-	0
D4	50	4.94 ± 0.02	5.02 ± 0.03	16.32 ± 0.03	16.53 ± 0.03	7.45 ± 0.03	7.50 ± 0.05	-	0
D5	50	4.94 ± 0.03	5.02 ± 0.03	16.31 ± 0.03	16.53 ± 0.03	7.45 ± 0.02	7.51 ± 0.06	-	0
D6	50	4.95 ± 0.02	5.01 ± 0.02	16.32 ± 0.03	16.53 ± 0.03	7.44 ± 0.04	7.51 ± 0.07	-	0
D7	40	4.94 ± 0.03	5.02 ± 0.03	16.31 ± 0.02	16.53 ± 0.03	7.45 ± 0.02	7.50 ± 0.08	-	0

D8	40	4.95 ± 0.02	5.01 ± 0.02	16.32 ± 0.03	16.53 ± 0.03	7.45 ± 0.03	7.50 ± 0.09	Edge breaking	3
D9	40	4.94 ± 0.03	5.01 ± 0.02	16.32 ± 0.03	16.53 ± 0.03	7.45 ± 0.03	7.50 ± 0.10	Logo intagliation	3

Figure 4.27: Tablet defects of 600 mg oval tablets



Edge breaking



Logo Intagliation

Discussion:

In oval 600 mg tablet, linear model was found to be significant. Coating of Oval 600 mg tablet was most critical as the major defect seen here was edge breaking and the values of many batches were on the unacceptable range of % RSD and % CPE. The pattern showed that pan speed had significant impact on Oval 600 mg tablet compared to spray rate as increasing the pan speed led to decrease in the value of %RSD.

With increase in pan rpm % RSD decreased and % CPE decreased minorly, infact oval 600 mg tablets showed lowest % CPE and highest % of RSD compared to all other shapes and strengths, so it is the least choice as compared to Round shape.

Optimized batch: Batch D2 with the spray rate of 3.5 g/min and pan speed of 14 rpm showed % RSD of 4 and % CPE of 84.3 %.

4.11.8 Check point batch analysis for Oval 600 mg tablets

4.11.8.1: Data for check point batch

Figure 4.28: Results of check point batch analysis for oval 600 mg tablet

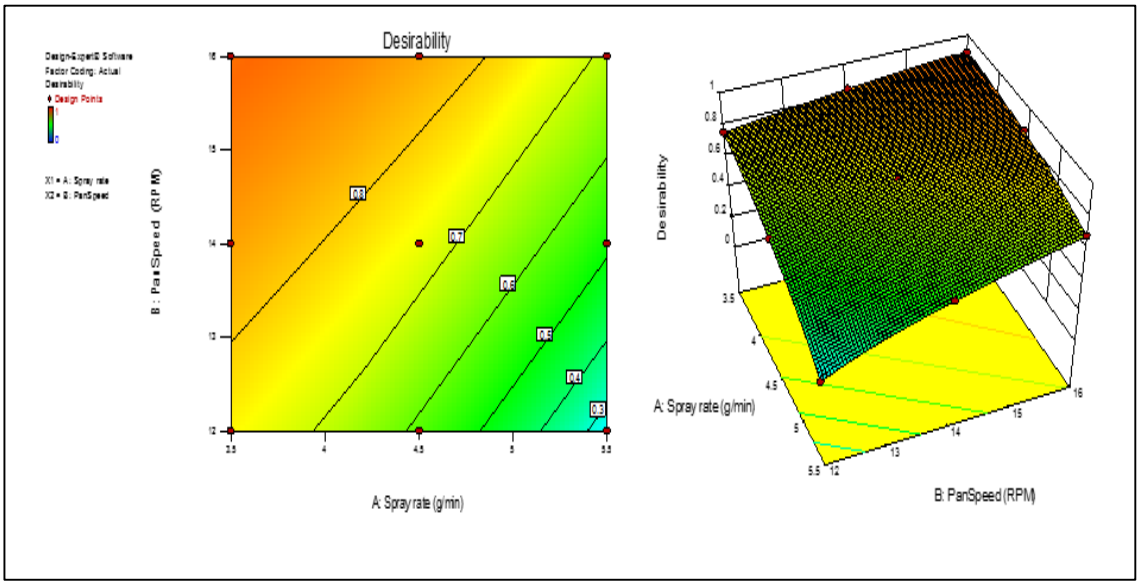


Table 4.54: Comparison between experimental and predicted values for check point of oval 600 mg tablets

Spray rate = 4 g/min	Pan Speed = 14rpm	
Parameters	**% RSD**	**% CPE**
Predicted	**4.504**	**84.997**
Experimental	**4.3**	**85.3**
Calculated	**0.167**	**0.146**
Tabulated	**6.313**	**6.313**

Discussion:

The models developed nearly same values as that of experimental values. So, this model can be said to be **validated** model for the given full factorial design.

4.12 COLOR CODING OF DoE BATCHES FOR COMPARATIVE STUDY

Table 4.55 Color coding for % RSD of all DoE batches of Round and Oval shape tablets

%RSD								
Batch	**Spray rate(g/min)**	**Pan speed (rpm)**	**Round 200**	**Round 600**	**Oval 200**	**Oval 600**	**Min**	**Max**
1	3.5	16/12	4	4.6	5.9	4.6	4	5.9
2	3.5	18/14	3.4	3.7	5.1	4	3.4	5.1
3	3.5	20/16	2.9	3.2	4.0	3.8	2.9	4.0
4	4.5	16/12	4.6	5.1	5.3	5.4	4.6	5.4
5	4.5	18/14	3.7	4.3	4.9	4.6	3.7	4.9
6	4.5	20/16	3.1	3.5	3.5	4.7	3.1	4.7
7	5.5	16/12	4.9	6.3	4.7	6.2	4.7	6.3
8	5.5	18/14	3.9	6.1	3.1	4.9	3.1	6.1
9	5.5	20/16	4.1	5.1	3.7	5	3.7	5.1

acceptable batch

Table 4.56 Color coding for % CPE of all DoE batches of Round and Oval shape tablets

% CPE								
Batch	**Spray rate (g/min)**	**Pan speed (rpm)**	**Round 200**	**Round 600**	**Oval 200**	**Oval 600**	**Min**	**Max**
1	3.5	16/12	94.2	92.9	81.6	84.9	81.6	94.2
2	3.5	18/14	97.5	94.3	87.1	84.3	84.3	97.5
3	3.5	20/16	97.6	96.7	91.8	84	84.0	97.6
4	4.5	16/12	92.6	92.1	85.9	85.2	85.2	92.6
5	4.5	18/14	96.1	93.0	89.5	84.9	84.9	96.1
6	4.5	20/16	98.3	94.1	96.1	84.6	84.6	98.3
7	5.5	16/12	90.5	89.4	90.9	86.0	86.0	90.9
8	5.5	18/14	94.3	90.6	97.5	85.8	85.8	97.5
9	5.5	20/16	94.6	91.2	94.4	85.4	85.4	94.6

acceptable batch

Discussion:

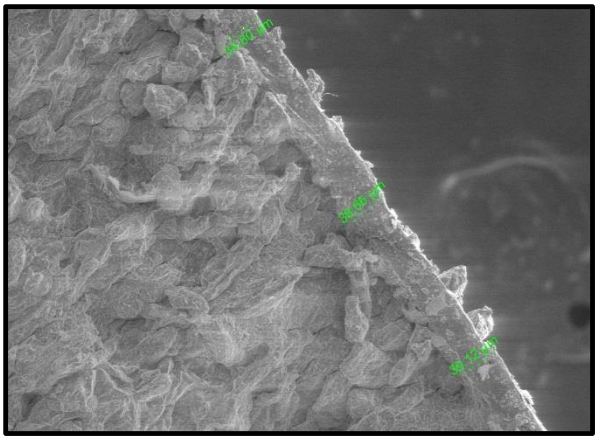
Here the color coding was given to compare the % RSD and % CPE results obtained of all the DoE batches to select best possible shape for API coating on core tablets. The comparison is done of batches considering same parameters. Minimum and maximum values of batches having same parameters are determined. The batch having minimum value of % RSD and maximum value of % CPE is considered as acceptable. From above color coding it was observed that 200 mg round shape tablets had highest no of batches having acceptable values followed by 200 mg oval. As 200 mg round tablet was selected as the best batch among all the batches, SEM analysis of round 200 mg batch was further performed.

4.13 SEM (Scanning Electron Microscopy) analysis of 200 mg round API coated tablet

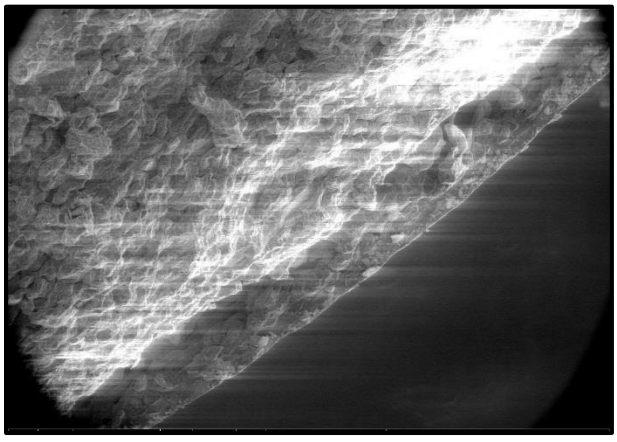
Procedure

SEM analysis of 200 mg round tablet having % RSD of assay of 3.1 and % CPE of 98.3 % was performed for surface analysis and film coating thickness of tablet using Scanning Electron Microscope XL 30 ESEM with EDAX: Resolution : upto 2 A^0; Acc. voltage: 30 kV;

Figure 4.29: Scanning Electron Microscopy showing the thickness of API film coat on core tablet



Magnification: 500x



Magnification: 250x

Discussion:

SEM analysis of optimized batch of 200 mg round tablets was performed to determine the thickness of API film coat applied on core tablet. The analysis showed uniformity in the thickness of coat.

4.14 Conclusion

- The results obtained were anticipated in many instances and there were instances in which the results obtained were equally unexpected.
- This results would almost certainly not have been obtained by conventional trial and error experiments.
- Work used prior knowledge and systemic approach with predefined objective i.e. the QbD approach to identify and interrogate the impact of variations in process parameters on product quality.
- The results show that **round shaped tablets are preferred over oval shape** tablet. In particular Round 200 mg tablets is the first choice of shape to be used for active film coating followed by oval 200, round 600 and oval 600.
- **Oval 600mg tablets** are less preferred as the main reason involved is **edge breaking** which is very prominent issue seen during various combination of spray rate and pan speed during active coating of tablet.
- Significant film thickness difference depending on the surface area of tablet is seen. For Round tablets, there is similarity in film thickness between face and the end of the tablet. This may not be serious issue for aesthetic coating but may be serious issue for coating actives on tablet.
- To ensure success in film coating process formulation together with design of tablet should be considered early in the development.

CHAPTER - 5

SUMMARY

5. SUMMARY

Coating is a common process used in manufacturing of tablet to provide protection to the tablet core, enhance the organoleptic characters and modify the release of tablets. Active film coating is a process that enables uniform film formation on the surface of core tablets by spraying the coating liquid containing an Active Pharmaceutical Ingredient (API) dissolved or dispersed in coating material. Manufacturing of low dose API with direct compression method, may have compressibility as well as compatibility issues. Using wet granulation method, loss of API might occur at many steps. This issue can be resolved by using the novel approach of active film coating. Active film coating is a process that enables uniform film formation on the surface of core tablets by spraying the coating liquid containing an API dissolved or dispersed in coating material. The uniformity of coating is a critical quality attribute as coated tablets have to pass the test of uniformity of dosage units according to the regulatory requirements

Variables which were studied to improve the coating efficiency of actives on tablets. The influence of important parameters on the active coating. Round and oval shaped tablets with two different weights 200mg and 600mg were formulated as core placebo tablets. Coating solution was prepared using model drug as an active (3 mg) and a low viscosity polymer HPMC E5 as a film forming polymer using water as solvent. Pan load, spray rate and pan rpm were identified as critical process parameters. Coating was performed and pan load was optimized in preliminary trials. Pan load of 800 g was optimized as the value of % RSD and % CPE were within the limits. Hence, further optimization of spray rate and pan rpm was done using 800 g of the pan load wherein spray rate and pan load were optimized by 3^2 full factorial design using Design Expert 9.0.4 software. %RSD and %CPE were taken as dependent variables. DoE trials were individually performed on all four types of tablets to explore maximum levels those could affect content uniformity (%RSD and AV value) and % CPE.

The results showed that pan speed had great influence on the quality of the film coated tablets produced in a side vented perforated pan coater, independent of size and shape of the tablet. The quality of the film improved with increasing pan speed. Increasing the pan speed decreased the value of % RSD. Hence, pan speed was considered as the main parameter which affected active film coating. On the basis of results obtained, round 200 mg tablets showed better coating uniformity and coating process efficiency as compared to other tablets. But there is an upper limit for the pan speed because with increasing pan speed the attrition will rise and also the incidence of breaking of edges will increase. It was concluded that changing the shape is first choice than changing the weight of tablet to achieve maximum coating uniformity and coating process efficiency. To ensure success in film coating process design of tablet along with formulation should be considered early in the development. Industrial applicability of the project lies in the tablet production of low dose API as well as for preparing fixed dose combination tablets (immediate release API can be coated on the core tablets having modified release profile). Active coating shows great potential for formulating actively coated tablets offering intellectual property advantage in future.

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