"Formulation Development and Optimization of Delayed Release Drug delivery system of a BCS class II drug"

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MASTER OF PHARMACY

IN

PHARMACEUTICAL TECHNOLOGY & BIOPHARMACEUTICS

BY

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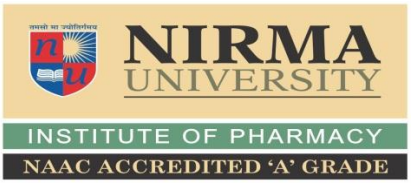

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May 2016

CERTIFICATE

This is to certify that the dissertation work entitled "Formulation Development and optimization of Delayed release drug release drug delivery system of a BCS class II drug" submitted by Mr. Yatin Jhamb with Regn. No. (14MPH120) 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 Pharmaceutical technology and Biopharmaceutis, Institute of Pharmacy, Nirma University 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 work entitled "Formulation Development and optimization of Delayed release drug release drug delivery system of a BCS class II drug", is based on the original work carried out by me under the guidance of Dr. Renuka Mishra, Assistant professor, Department of Pharmaceutical technology and Biopharmaceutics, Institute of Pharmacy, Nirma University and Mr. Sanjay C Wagh, Director, Lupin Research Park, Pune. 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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Mr. Yatin Jhamb

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LIST OF ABBREVIATIONS

Sr. No.	Abbreviations	Full form
1	CCS	Croscarmellose sodium
2	CD	Cyclodextrin
3	CQA	Critical Quality Attributes
4	CR	Child Resistance
5	DCM	Dichloromethane
6	DS	Drug substance
7	HDPE	High Density Polyethylene
8	HPC	Hydroxypropyl cellulose
9	MCC	Microcrystalline cellulose
10	OGD	Office of generic drug
11	PEG	Polyethylene Glycols
12	PSD	Particle size distribution
13	PVP	Polyvinyl Pyrrolidine
14	QTPP	Quality Target Product Profile
15	R	Reference
16	RLD	Reference listed drug
17	SD	Solid Dispersion
18	T_g	Glass transition temperature

1.0 Aim of the Present Work

1.1. Aim

Poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Drugs which have dissolution rate limited gastrointestinal has shown improved bioavailability when reduction of particle size is done. However, size reduction has also shown aggregation and agglomeration of small particles and results in poor wettability. Preparation of solid dispersions of these drugs using water soluble carriers results in overcoming these problems and help in increased dissolution. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcomes the limitations of other approaches employed for solubility enhancement such as salt formation, solubilisation by co-solvents, and particle size reduction. Studies have revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. Most of the work done suggests that solid dispersion involve drugs that poorly soluble in water and are highly permeable to the membranes and their rate limiting step is drug dissolution. On the basis of these studies, it is hypothesized that the rate of in vivo absorption will be concurrently accelerated with an increase in the rate of drug dissolution. Solid dispersion technique is used to increase the aqueous solubility of drugs that have low aqueous solubility and high permeability. These types of drugs are called Class II drugs as per Biopharmaceutical Classification System (BCS).

The aim is to prepare generic tablet of a patented tablet formulation and show similar dissolution profile as of reference formulation. The formulation prepared is a delayed release tablet, the formulation is such that the tablet will not release or release a negligible amount of drug in the stomach pH and it will release its entire drug in the intestinal pH. This drug delivery system is prepared by using solid dispersion technology, in which a pH dependent polymer is used which has ability to increase the wettability of the drug and hence increase its solubility along its enteric property. To achieve above stated goal different technologies were applied such as Top spray,

Wurter Coating in GPCG 1.1, Rapid mixer granulator, Rotary evaporator, and Spray drying.

1.2. Rationale behind delayed release formulation

Rapid dissolution rates that result in increased bioavailability and reduction in pre-systemic metabolism. The latter advantage may occur due to saturation of the enzyme responsible for biotransformation of the drug or inhibition of the enzyme by the carrier. The use of a solid dispersion of selected polymer with low solubility drug can help to produce a supersaturated solution in-vivo to ensure adequate bioavailability.

2.0 Introduction [1-4]

2.1. Introduction to Solid Dispersions

For commercial production, three most successful methods used for solid dispersion preparation are melt extrusion, spray drying and co-precipitation. Historically solid dispersion is defined as a dispersion of drug in a solid matrix, where the matrix is either a small molecular or polymer. The dispersed state could be of any form for example eutectic mixture, crystalline/glass solution, and amorphous/ crystalline suspension. The most popular kind of solid dispersion among the pharmaceutical scientists is amorphous polymer matrix in which the drug is preferably molecularly dispersed. The drug-polymer interaction is the key to understand the most important issues that arise while dealing with solid dispersion viz. the drug loading, stability of the system and its dissolution performance.

In 1961, Sekiguchi and Obi developed a practical method whereby most of the limitations with the bioavailability enhancement of poorly water soluble drugs could be overcome. This approach is known as "Solid Dispersion" approach.

Chiou and Riegelman defined the term solid dispersion as "a dispersion involving the formulation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures." The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of the drug development. Many techniques are used to increase the dissolution rate and thereby oral bioavailability of such drugs. These include salt formation, Co-solubilisation and particle size reduction. Salt formation of neutral compound is not possible and salt formation of weakly acidic and weakly basic drug is not practically successful. Even when the salt can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. By the use of surfactants and co-solvents, the solubilization of drugs in organic solvents or in aqueous media leads to liquid formulations which are usually undesirable and may have problems related to patient acceptability and commercialization. Particle size reduction is also one of the commonly used techniques to increase the dissolution rate, but there is also a practical limitation to this technique when it is achieved by methods like controlled

crystallization, grinding, pearl milling etc. the use of very fine powders in a dosage form may also be problematic because of handling issues and poor wettability due to charge development. When a solid dispersion or solid solution is used, a portion of drug dissolves immediately to saturate the GI fluid and the excess drug precipitates out as fine colloidal particles or oily globules of submicron size. Hence, owing to increase in the bioavailability of poor water-soluble drugs, solid dispersion has become one of the most active areas of research in the pharmaceutical arena.

2.2. Definition and types of solid dispersions [5- 8]

2.2.1. Definition

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution rate or sustained release of drug, altered solid state properties as well as improved stability.

Types of Solid Dispersions:

A) Simple Eutectic Mixture:

Eutectic mixture of a sparingly water-soluble drug and a highly hydrophilic carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline components (Figure. 1). These systems are usually prepared by melt fusion method. When this mixture is come in contact with water, the soluble carrier dissolves and leaves the drug in a microcrystalline state which gets solubilized rapidly. The increased rate of dissolution is due to increase in surface area.

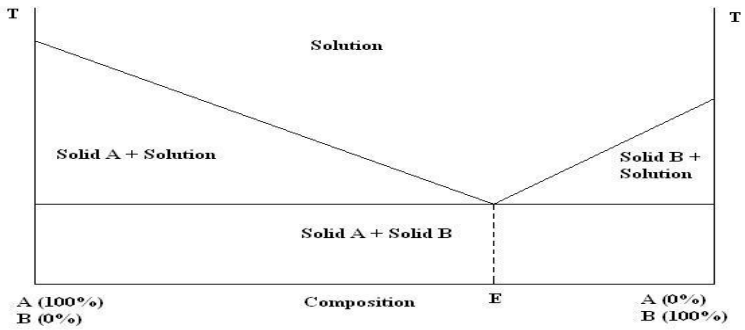

Figure 1: Hypothetical Phase Diagram of Eutectic Mixture

B) Solid Solutions:

Solid solutions consist of a solid solute dissolved in a solid solvent. This type of systems can be prepared by solvent evaporation or co-precipitation method, where guest solute and carrier are dissolved in a common volatile solvent such as alcohol. The solvent is allowed to evaporate, preferably by flash evaporation. As a result, a mixed crystal containing amorphous drug in crystalline carrier is formed because the two components crystallize together in a homogenous single phase system. Such dispersions are also known as "Co-precipitates" or "Co-evaporates". This system would be expected to yield much higher rates of dissolution than simple eutectic systems. Because, the basic difference between solid solution and eutectic mixture is that the drug is precipitated out in an amorphous form in solid dispersion/solution while it is in crystalline form in eutectic mixture. Solid solution can be classified as per their extent of miscibility between the two components or the crystalline structure of the solid solution.

(i) Continuous solid solutions

(ii) Discontinuous solid solution

(iii) Substitutional solid solution

(iv) Interstitial solid solution

i) Continuous Solid Solutions:

In this type of system, both the components should be miscible or soluble at solid state in all proportions (Figure.2). No solid solution of this type has shown faster dissolution properties, however it is theoretically possible. It is a rule of thumb that a faster dissolution rate would be achieved if the drug is present in less amount. Though, the small amount of the soluble carrier in the crystalline lattice of the poorly soluble drugs is also capable of showing a dissolution rate faster than the pure compound with similar particle size.

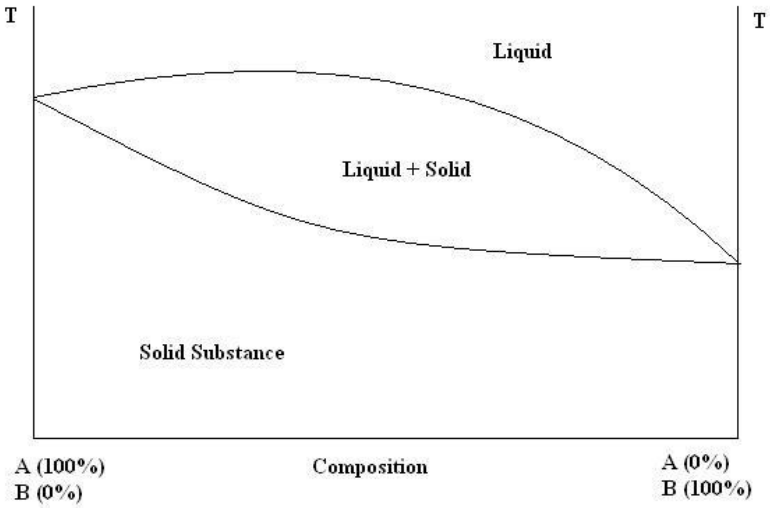

Figure. 2: Hypothetical Phase Diagram of Continuous Solid Solution

ii) Discontinuous Solid Solution:

In this system (Figure. 3), in contrast to the continuous solid solution, there is only a limited solubility of a solute in a solid solvent. Each component has the ability of dissolving the other to a some extent above the eutectic temperature. However, as the temperature is lowered, the solid solution window becomes narrower. The free energy of stable and limited solid solutions is lesser than that of pure solvent.

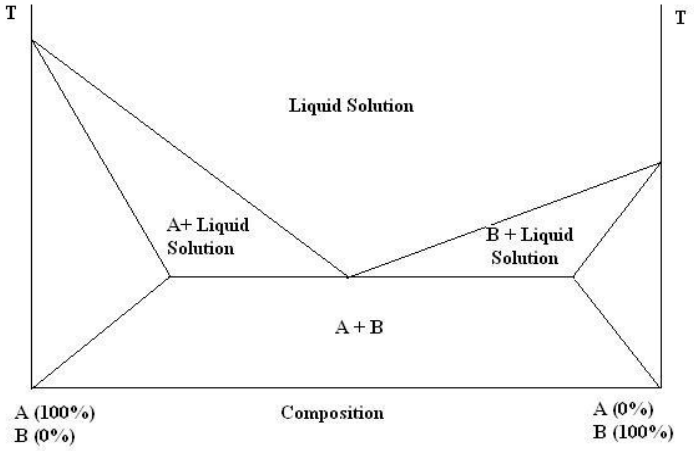

Figure 3: Hypothetical Phase Diagram of Discontinuous Solid Solution

iii) Substitutional Solid Solution:

As shown in Figure.4, in this solid solution, the solute molecule substitutes for the solvent molecules in the crystal lattice of the solid solvent. It can form both type of solid solution i.e. a continuous or discontinuous solid solution. The size and steric effect of the solute molecules has a vital role in the formation of solid solution. The size difference of the solute and the solvent molecule should be very less.

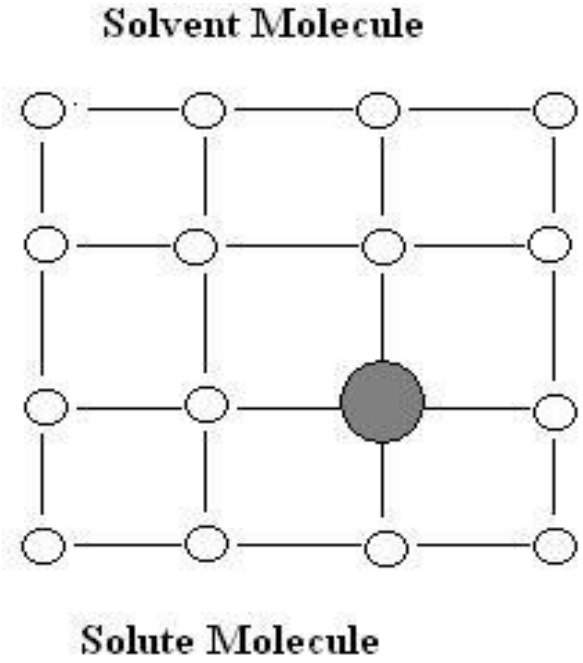

Figure 4: Substitutional Solid Solution

iv) Interstitial Solid Solution:

The solute molecule goes into the interstitial space of the solvent lattice (Figure.5). This results in a discontinuous (limited) solid solution. The size of the solute is vital in order to get inside the interstitial spaces. It was proved that apparent diameter of the solute molecules should be less than that of the solvent in order to obtain an extensive interstitial solid solution of metals.

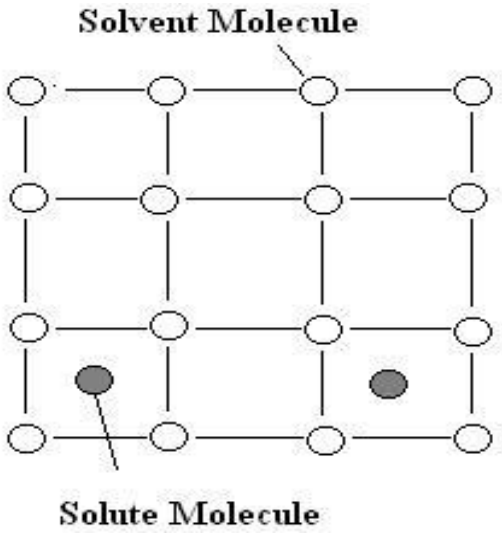

Figure 5: Interstitial Solid Solution

C) Glass Solution:

It is a homogenous system in which a glassy or a vitreous carrier solubilizes drug molecules in its matrix. Polyvinylpyrolidone dissolved in organic solvents which undergoes a phase transition to a glassy state upon evaporation of the solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature (T_g). On heating, it softens progressively without a sharp melting point.

D) Compound or Complex Formation:

This type of system is characterized by complex formation of two components in a binary system during solid dispersion preparation. The availability of drug from complex or compound depends on their solubility, association constant and intrinsic absorption rate of complex. Rate of dissolution and gastrointestinal absorption can be increased by the formation of a hydrophilic complex which has low association constant.

E) Amorphous Precipitation:

It occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system is generally responsible for much greater dissolution rates than the corresponding crystalline forms of the drug. It is

hypothesised that a drug with high super cooling property has more tendency to solidify as an amorphous form in the presence of a carrier. therefore, amorphous precipitation is rarely observed.

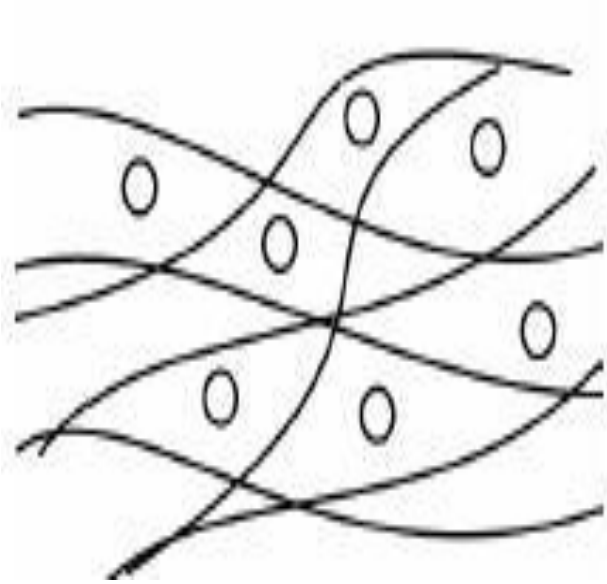

Figure 6: Amorphous Precipitation

2.2.2. Mechanism of dissolution rate enhancement [9,10]

The increase in drug dissolution rate from solid dispersion system can be because of a number of factors like particle size, crystalline or polymorphic forms and wettability of drug etc. It is not easy to prove experimentally that any one particular factor is more important than another. The main reasons postulated for the observed improvements in dissolution from these systems are as follows:

a) Reduction of Particle Size:

In case of glass solution, solid solution and amorphous dispersions, particle size is reduced. This may result in enhanced dissolution rate due to increase in the surface area. Similarly, it has been suggested that particles exposed to dissolution medium as physically separate entities may reduce aggregation.

b) Solubilization Effect:

The carrier material, as it dissolves, may have solubilization effect on the drug. Enhancement in solubility and dissolution rate of poorly soluble drugs is related to the ability of carrier matrix to improve local drug solubility as well as wettability.

c) Wettability and Dispersibility:

The carrier may also show intrensing effect on the wettability and dispersibility of the drug because of the surfactant action. Decreasing the interfacial tension among hydrophobic drug particle and aqueous solvent phase, increasing the effective surface area which is in contact to the dissolution medium. This also decreases agglomeration or aggregation of the particles, which can slow down the dissolution.

d) Conversion of Polymorphic Nature of Solute:

Energy required to transfer a molecule from crystal lattice of a purely crystalline solid is greater than that required for non-crystalline (amorphous) solid. Hence amorphous state of a substance shows higher dissolution rates. But the amorphous solids also demonstrate lack of physical stability due to natural tendency to form crystals. Thus formation of metastable dispersions with reduced lattice energy would result in faster dissolution rate and comparatively acceptable stability.

2.2.3. Selection of carrier [11, 12]

One of the most important steps in the formulation and development of solid dispersion for various applications is selection of carrier. The properties of carrier have a major influence on dissolution characteristics of the drug. A material should possess following characteristics to be suitable carrier for increasing dissolution:

i. Freely water-soluble with intrinsic rapid dissolution properties
ii. It should be non-toxic nature and pharmacologically inert.
iii. It should be heat stable preferably with low melting point especially for melt method
iv. Soluble in a different solvents and should pass through a vitreous state upon solvent evaporation for the solvent evaporation technique.
v. Should be capable of increasing the aqueous solubility of the drug
vi. Chemically compatible and should not form a strongly bonded complex with drug.

2.2.4. POLYMERS USED IN SOLID DISPERSIONS

A number of polymers can be used as carriers for preparing solid dispersion. Table1 represents various types and examples of carriers. Some polymers used in solid dispersions are as follows:

A) Polyethylene Glycols (PEG):

Polyethylene glycol refers to compounds that are prepared by reacting ethylene glycol with ethylene oxide. PEGs with molecular weight more than 300,000 are generally known as polyethylene oxides.

B) Polyvinyl Pyrrolidone (PVP):

PVPs have molecular weights ranging from 10,000 to 700,000. It is soluble in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP is not labile for preparing solid dispersions which are formulated by melt method because it melts at a very high temperature above 275ºC, where it gets decomposed.

C) Polymers and Surface Active Agent Combinations:

To lowers the interfacial tension between drug and dissolution medium the surfactants can be added and promotes the wetting of the drug hence results in enhanced solubility and dissolution of drug. In general ternary dispersion systems have higher dissolution rate than binary dispersion systems.

D) Cyclodextrins:

Cyclodextrin (CD) are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment of hydrophobic solute in hydrophilic cavity of CD. Advantages of CD include increasing the stability of the drug, release profile during gastrointestinal transit through modification of drug release site and time profile, decreasing local tissue irritation and masking unpleasant taste.

E) Phospholipids:

Phospholipids are major structural components of cell membranes. Phosphotidylcholine was first isolated from egg yolk and brain. In phosphatidyl ethanolamine and phosphatidyl serine, the choline moiety is replaced by ethanolamine and serine respectively. Other phospholipids that occur in tissues include phosphotidyl ethanolamide, phosphotidyl serine and phosphotidyl glycerol. Naturally occuring lecithins contain both a saturated fatty acid and unsaturated fatty acids with some exceptions. Some of the polymers used for solid dispersions are listed in Table1.

Table1: Materials used as carrier for solid dispersion

S. No.	Category	Examples
1	Sugars	Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Xylitol, Mannitol, Lactose
2	Acids	Citric acid, Succinic Acid
3	Polymeric materials	PVP, PEG , Celluloses like HPMC,
		HEC, HPC, Pectin, Galactomannan, CDs
4	Insoluble/ enteric polymer	HPMC Phthalate, Polymethacrylates
		Polyoxyethylene stearate, Polyoxyethylene Alkyl Ethers,
5	Surfactants	Poloxamers, , Deoxycholic acid,
		Tween, Span
		Pentaerythritol, Pentaerythrityl tetra acetate.
6	Miscellaneous	Urea, Urethane, Hydroxy alkyl xanthins

2.2.5 Methods of preparation of solid dispersions [13- 16]

A) Fusion Process:

This process is technically easier method of formulate solid dispersions provided that the drug and carrier are miscible in the molten state. Drug and carrier mixture of eutectic composition is molten at temperature above its eutectic temperature. Then molten mass is solidified in cold condition such as on an ice bath and pulverized to a powder. super saturation of the drug can be obtained by quenching the melt rapidly, rapid congealing is favoured. The solidification is done on stainless steel plates so that it helps in rapid temperature loss. A modification of the process involves spray congealing from a modified spray drier onto cold metal surface. Decomposition should be avoided while fusion but it is dependent on composition and affected by fusion time, temperature and rate of cooling. Hence, to withhold drug content andphysicochemical stability of preparation at an acceptable level, fusion must be effected at a temperature only just in excess of that which completely melts both drug and carrier.

B) Solvent Evaporation Process:

Solid dispersion prepared by solvent removal process was termed by Bates et al. as "Coprecipitates". But these systems should more correctly, be designated as "Coevaporate", a term that has been recently adopted.

The solvent solvents used in evaporation process are organic solvent, the agent to intimately mix the drug and carrier molecules and was initially used by Tachibana and Nakamura, where, chloroform was used to co-dissolve β-carotene and PVP to form Co-evaporate.

The selection of solvent and its rate of removal are important parameters affecting the quality of the solid dispersion. Since the selected carriers are generally water soluble and the drugs are hydrophobic, the selection of a common solvent is difficult and its complete removal, necessitated by its toxic nature, is imperative. Vacuum evaporation may be used for solvent removal at low temperature and also at a controlled rate. Faster removal of the solvent may be achieved by lyophilisation. The difficulties in

selecting a common solvent to both drug and carrier may be overcome by using an azeotropic mixture of solvent in water.

C) Fusion Solvent Method:

This method consists of dissolving the drug in a suitable solvent and incorporating the solution directly in the melt of carrier. If the carrier is capable of holding a certain proportion of liquid yet maintains its solid properties and if the liquid is innocuous, then the need for solvent removal is eliminated. This method is particularly useful for drugs that have high melting points or are thermo-labile.

D) Supercritical Fluid Process:

Supercritical CO2 is a good solvent for Hydrophobic as well as hydrophilic components under suitable conditions of temperature and pressure. Therefore, it has ability as an alternative for conventional organic solvents used in solvent based processes for forming solid dispersions because of its favourable characteristics of

being non-toxic and inexpensive. The process consists of the following steps:

i. Charging the bioactive material and suitable polymer into the autoclave.

ii. Addition of supercritical CO_2 under precise conditions of temperature and pressure, that causes polymer to swell

iii. Mechanical stirring in the autoclave

iv. Computerized Rapid depressurization of the autoclave vessel, controlled orifice to obtain desired particle size.

The temperature condition used in this process is fairly mild (35-75°C), which allows handling of heat sensitive biomolecules, such as enzymes and proteins.

2.2.6 Advantages and disadvantages of solid dispersions [17- 19]

The rapid dissolution rates is the main advantages of solid dispersion that result in improved bioavailability and reduction in pre-systemic metabolism. The latter advantage may occur due to saturation of the enzyme responsible for biotransformation of the drug or inhibition of the enzyme by the carrier, as in the case of morphine-tristearin dispersion. Both can lead to the need for lower dose of the drug. Other advantages include transformation of the liquid form of the drug into a solid form (e.g. clofibrate and benzoyl benzoate can be incorporated into PEG 6000 to give a solid, avoiding polymorphic changes and thereby bioavailability problems) and protection of certain drugs by PEGs against decomposition by saliva to allow buccal absorption.

The disadvantages of solid dispersion are can be seen due to stability problem. Many systems have shown that changes in crystallinity and reduction in dissolution rate with aging. Moisture and temperature are critical in deteriorating effect on solid dispersions than on physical mixtures. Some solid dispersion may even show tackiness.

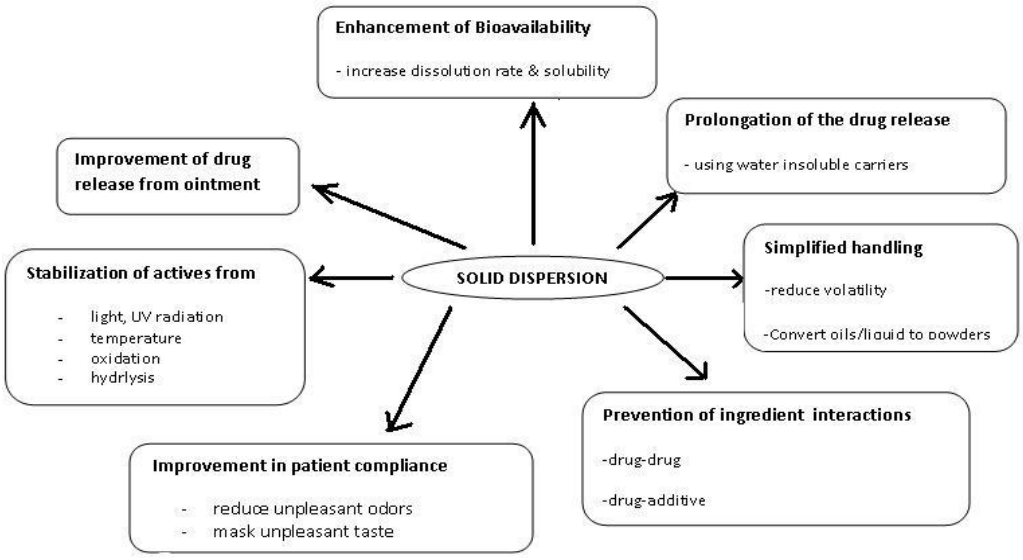

Figure 7: Pharmaceutical Applications of Solid Dispersion

3.0. Literature Review

T. Vasconcelos, et al[21] stated that amorphous products and particularly amorphous solid dispersions are one of the most exciting areas in the pharmaceutical field. This approach has advantages over other in improving bioavailability. Different processes are reviewed and have shown rationale for their selection from lab scale to industrial scale up for development of solid dispersion.

Shergill Mandip et al[22] demonstrated development and characterization of sustained release of disulfiram solid. Kolliphor P188 and P237 (prepared by Kollidon SR and HPMC) were used as polymer.by using hot melt technology at 80oC. The drug loading capacity of polymer was between 43% and 46% and the drug was in amorphous state. The release rate of drug is manipulated by both loading and type and amount of sustained release polymer used. Though, HPMC has shown faster release profile than Kollidon SR.

S. Baghel et al[23] focused on key aspects of polymeric amorphous solid dispersion. It is concluded that a better knowledge of thermodynamics along with molecular level processes such as molecular mobility, devitrification, glass transition temperature, fragility and molecular interaction of drug-polymer is crucial for formulating an efficient and stable amorphous drug delivery system.

Zhao Yang et al[24] studied nimodipine solid dosage form and stated that nimodipine has poor bioavailability. To solve this limitation of the solid dosage form of the nimodipine solid dispersion is prepared. The polymer used for preparing solid dispersion is HPMC-AS. Dissolution studies have shown that the drug release is retarded in stomach pH and release in the intestinal pH and resulting in high dissolution and hence increase bioavailability of the nimodipine.

4.0. Experimental section

1. Materials and reagents

a) Drug Characterization
b) Reference product Characterization
c) Pre-formulation study
d) Formulation optimization of the product
e) Analytical characterization
f) Stability studies of optimized formulation

2. Apparatus/ Instrumentation etc.

Selection of Drug and Excipients

Based on Reference product evaluation, similar excipients were selected for the product development. The decision on selection of specific excipient was further supported based on the results of excipient compatibility studies.

Table 2: Selection of Drug and Excipients

S. No.	Ingredients	Vender	Use/Class
1	Drug substance –ABC	PQR	BCS Class II
2	Functional polymer	XYZ	Polymer
3	Methylene chloride	SDFCL	Solvent
4	Methanol	SDFCL	Solvent
5	Microcrystalline cellulose (Avicel PH 101,102,112,200,301)	FMC	Diluent
6	Hydrooxy propyl cellulose (EXF Pharm)	Ashland	Binder
7	Croscarmellose sodium	FMC	Disintegrant
8	Colloidal silicon dioxide (Aerosil 200)	Evonik	Glidant
9	Magnesium stearate	Merck	Lubricant
10	Opadry II yellow	Colorcon	Coating agent

4.1. Methodology and Experimental work

4.1.1 Drug Characterization

4.1.2 Drug substance pharmacokinetic characterization

4.1.2.1. Physicochemical characterization

Table 3: Physicochemical characterization of drug

Physicochemical Properties	
Drug substance	ABC
BCS Class	II
Protein binding	Highly protein bound (>98%), predominantly to albumin
Description	Off-white colour powder
Aqueous Solubility	0.027 mg/L at 25 ℃
Organic solubility	Soluble in Dichloromethane
PARTICLE SIZE DISTRIBUTION (MALVERN)	
D10	4.1 µm
D50	54.2 µm
D90	208.3 µm

Characterization of Drug substance (DS)

1) Particle size distribution (PSD)

These parameters are not critical since the drug substance to be dissolved in organic solvents and processed further, hence PSD need not to be evaluated.

2) Density (Bulk and Tapped) and flowability

These parameters are not critical since the drug substance to be dissolved in organic solvents and processed further, hence BD/TD need not to be evaluated.

3) Aqueous Solubility as a function of pH

Drug is soluble in Dichloromethane and practically insoluble in water. The aqueous solubility of drug as a function of pH is given in Table 4 and Table 5 respectively.

Table 4: Solubility of Drug in different pH aqueous solution

Media	Results
pH 1.2 Solution (Hydrochloric acid buffer)	10 mg/100 mL (Insoluble)
pH 3.0 Solution (Acid Phthalate Buffer)	10 mg/100 mL (Insoluble)
pH 4.5 Solution (Acetate buffer)	10 mg/100 mL (Insoluble)
pH 6.8 Solution (Phosphate buffer)	10 mg/100 mL (Insoluble)
pH 7.2 Solution (Phosphate buffer)	10 mg/100 mL (Insoluble)
pH 8.0 Solution (Phosphate buffer)	10 mg/100 mL (Insoluble)

Table 5: Solubility of drug in different pH (As per in-house determination) aqueous solution

Media	Mean Solubility (mg/mL)	Actual pH of medium	Mean Observed pH of medium	Volume of Media Required to Dissolve Highest Dose (100.0 mg)
0.1 N Hydrochloric Acid (pH 1.2)	1.199	1.22	1.36	83.40
0.01N Hydrochloric Acid (pH 2.0)	0.045	2.04	2.11	2222.22
pH 4.5 Acetate Buffer	0	4.52	4.78	Not applicable
pH 6.8 Phosphate Buffer	0	6.77	6.86	Not applicable

Conclusions:

Drug exhibits pH-dependent solubility. Based on solubility data and BCS solubility criteria, it is concluded that drug exhibits low solubility in the all physiological pH range except pH 1.2.

4) Partition coefficient

Partition coefficient in n-octanol/pH 7.4 solution is +2.54. This is intrinsic property of drug substance.

5) Melting range

Table 6:The melting range for three batches of Drug.

Batch Number	Melting range(°C)
ABC Lot I	166.5-167.9
ABC Lot II	166.2-168.2
ABC Lot III	166.7-169.3

6) Chemical stability in solid state

The results of six months accelerated and eighteen months long term stability study data shows that there is no significant change in any of the parameters of drug.

Storage condition: Preserve in well closed containers at controlled room temperature between 20°C and 25°C (excursions allowed between 15°C and 30°C).

Table 7: Reference product characterization

Drug substance	ABC
BCS Class	II

Table 8: Physicochemical characterization of Active Pharmaceutical Ingredient (Drug)

Sr. No.	TEST	OBSERVATION
1	Description	Off-white colour powder
2	Solubility	Complies
3	Water content by KFR	0.43% w/w
4	Assay by HPLC	99.6% w/w
5	**Solubility of Drug in physiological media**	
	0.1 N HCl	1.199
	0.01 N HCl	0.045
	pH 4..8 Acetate buffer	0
	Sodium Phosphate buffer pH 6.8	0
	Sodium Phosphate buffer pH 6.8 + 0.37% Tween 80	0.016

4.2. Reference product characterization

Table 9: Reference product dosage form information

S. No	Parameters	Details
1	**Dosage form**	Tablet
2	**Dosage design**	Delayed release tablet
3	**Route of administration**	Oral
4	**Container closure system**	HDPE Bottle with CRC.
5	**Storage Condition**	Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F)

4.3. Pre-formulation study

To study the compatibility of the excipients with Drug substance, drug-excipient compatibility studies were undertaken for drug substance with different excipients. During the course of study, any change in degradation product profile was monitored. Drug substance and individual excipients were mixed in a predetermined ratio using mortar and pestle. The triturated blend was transferred to glass vials capped with LDPE plug with two holes (open condition) and Rubber closure sealed with aluminium seal (closed condition). The samples were then kept under accelerated condition of 40 ℃/ 75 % RH up to 1 month.

Table 10: Drug Excipient compatibility study

S. No.	Name of the Excipients / Drug Substance	Application Category	Observation	
			Initial	After 30 days
1	Drug(X)	Drug	No change	No change
2	Drug(X)+ Functional polymer	Polymer	No change	No change
3	Drug(X)+ Microcrystalline cellulose	Diluent	No change	No change
4	Drug(X)+ Hydrooxy propyl cellulose	Binder	No change	No change
5	Drug(X)+ Colloidal silicon dioxide -200	Glident	No change	No change
6	Drug(X)+ Crosscarmellose sodium	Disitegrant	No change	No change
7	Drug(X)+ Mag-stearate	Lubricant	No change	No change
8	Drug(X)+ Opadry II yellow		No change	No change
Pack				
Glass Vials closed with rubber stopper sealed with Aluminum seal (CLOSED)				
Glass Vials closed with LDPE plug pierced with small holes (OPEN)				
Storagecondition		**Studyduration**		**Testing frequency**
40^0 C/75% RH		Up to 30 days		Initial & 1 month

ACC: Accelerated condition - 40°C/75 % RH; M-Mont

Drug-Excipient compatibility results did not show significantly higher degradation products at 1M 40°C/75%RH storage condition when compared with the drug substance.

4.4. Materials and Methods

4.4.1. Materials

Table 11: Justification for selection of excipients

S. No.	Name of the Chemical	Manufacturer / Supplier	Function/Class	Rationale for selection
1	Drug ABC	PQR	BCS Class II	Active pharmaceutical ingredient
2	Functional polymer	XYZ	Enteric polymer	It is pH sensitive polymer which dissolve in intestinal pH and is insoluble in stomach pH so it is used as enteric polymer. It also enhance solubility of drug in intestinal pH.
3	Microcrystalline cellulose	FMC Biopolymer	Diluent	It acts as diluent in test formulation. Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a diluent in oral tablet and capsule formulations where it is used in 20–90% concentration range.
4	Crosscarmellose sodium	Nippon	Disintegrant	It acts as disintegrant in test formulation. Croscarmellose sodium is a water-insoluble tablet disintegrant used in 2-5% concentration range. The selected grade is larger particles size grade which provide a faster disintegration.
5	Hydroxy Propyl cellulose	Nippon soda	Binder	It acts as binder. Concentrations of hydroxy propyl cellulose of 2–6% w/w may be used as a binder in either wet granulation or dry, direct compression tableting processes.
6	Colloidal silicon dioxide NF	Evonik Degussa	Glidant	It acts as glidant in test formulation. It is widely used glidant in concentration range of 0.1 – 1.0% Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry granules.

S. No.	Name of the Chemical	Manufacturer / Supplier	Function/Class	Rationale for selection
7	Magnesium Stearate NF	Merck	Lubricant	It acts as lubricant in test formulation. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 - 5.0% w/w.
8	Opadry-II yellow	Colorcon	Coating material	It acts as coating agent in test formulation. Selected grade is generally used for moisture protection.

MCC: Microcrystalline cellulose; CCS: Croscarmellose sodium

4.5. Apparatus/ Instrumentation

4.5.1. Fluid Bed Granulation

Fluidization is the unit operation by which fine solids are transformed into a fluid like state through contact with a gas. At certain gas velocities, the fluid will support the particles, giving them freedom of mobility without entrainment. Such a fluidized bed resembles a vigorously boiling fluid, with solid particles undergoing extremely turbulent motion, which increases with gas velocity. Fluidized bed granulation is a process by which granules are produced in a single piece of equipment by spraying a binder solution on to a fluidized powder bed. This process is sometimes classified as the one-pot system.

4.5.2. Rotary Evaporation: The "Rotovap"

The rotovap works by increasing the rate of evaporation of the solvent by (1) reducing the pressure to lower the solvent boiling point, (2) rotating the sample to increase the effective surface area and (3) heating the solution.

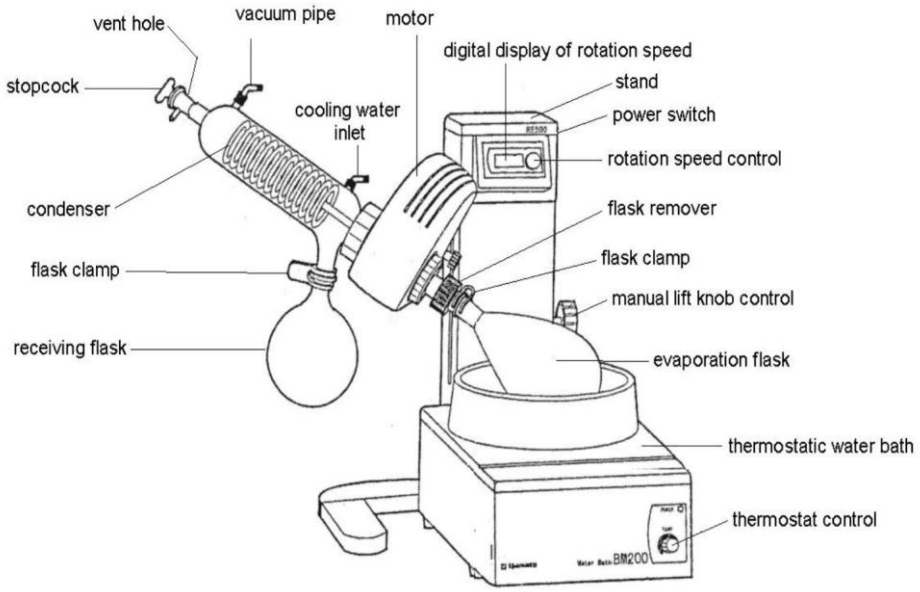

Figure 8. Typical rotary evaporator setup

A rotary evaporator is a specially designed instrument for the evaporation of solvent (single-stage or straight distillation) under vacuum. The evaporator consists of a heating bath with a rotating flask, in which the liquid is distributed as a thin film over the hot wall surfaces and can evaporate easily. The evaporation rate is regulated by the heating bath temperature, the size of flask, the pressure of distillation and the speed of rotation.

Table 12: Different parts and their process of fluid bed processor

S. No.	Part	Process/ working
1	Evaporation part	The solvent is heated via the heating bath. A thin film of solvent forms on the inner surface of the rotating evaporating flask, resulting in a higher rate of evaporation. Rotation ensures homogenous mixing of the sample and prevents overheating inside the flask.
2	Rotary drive	The drive unit provides constant rotation of the evaporating flask for the reasons stated above
3	Condensation part	The solvent vapor flows at high speed into the condensation part (condenser) of the rotary evaporator. At this point the energy inside the solvent vapor is transferred to the cooling medium (usually water) and the solvent condenses. The condensed solvent now flows by force of gravity into the receiving flask.
4	Receiving flask	The receiving flask is used to collect the condensed solvent.
5	Vacuum	Vacuum is used to lower the boiling temperature and hence raise the efficiency of the distillation process.
6	Advantages of the rotary evaporator (compared with static apparatus)	With a vacuum rotary evaporator you can carry out single-stage distillation runs quickly and gently. The evaporation capacity of a rotary evaporator is about 4 times greater than that of a conventional, static distillation apparatus. Heat transmission in the heating bath as well as inside the flask is greatly improved by rotation of the evaporating flask. Rotation greatly enlarges the active surface inside the flask, hastening the evaporation. With the liquid remaining at any one point of the flask wall for a short time only, it is subject to minimum stress during the distillation (no overheating, no incrustation). Bumping and foaming are greatly reduced by the rotation.

4.5.3 Spray Drying

Spray drying is one of the oldest forms of drying and one of the few technologies available for the conversion of a liquid, slurry, or low-viscosity paste to a dry solid (free-flowing powder) in one unit operation.

Figure 9 Typical Spray Drying setup.

5.0 Results and discussion

Reference product dissolution data

Dissolution of Drug Substance from the tablet is the rate limiting step for absorption of drug. For this reason, the dissolution pattern of reference product was thoroughly evaluated. The factors investigated include the effect of different rotation speed. As OGD recommended dissolution method for X tablet is available, hence it was selected for comparative dissolution testing of the reference product and is described in Table 13.

Table 13: In-vitro dissolution test method for reference tablet as per dissolution method database

Drug Name	Dosage form	USP Apparatus	Speed (RPM)	Medium	Volume (ml)	Time (min)
ABC	Tablets	Type II (Paddle)	75	**Acid Stage**: 0.01 N HCl **Buffer Stage**: pH 6.8 with 0.37 % Polysorbate 80	Acid Stage: 750 mL; Buffer Stage 1000 mL	Acid Stage: 120; Buffer Stage: 10, 20, 30, 45 and 60.

The dissolution studies of reference Tablet was carried out as per method described for reference listed drug and the dissolution data obtained is presented in Table 14.The graphical data is represented in Figure 10.

Table 14: In-vitro dissolution test method of Reference product at different time points and at different pH media

Media	Time (min)	%Release
Acid Stage: 0.01N HCl	120	4
Followed by Buffer stage: pH 6.8 Phosphate buffer with 0.37% Tween 80	130	99
	140	101
	150	104
	165	102
	180	104

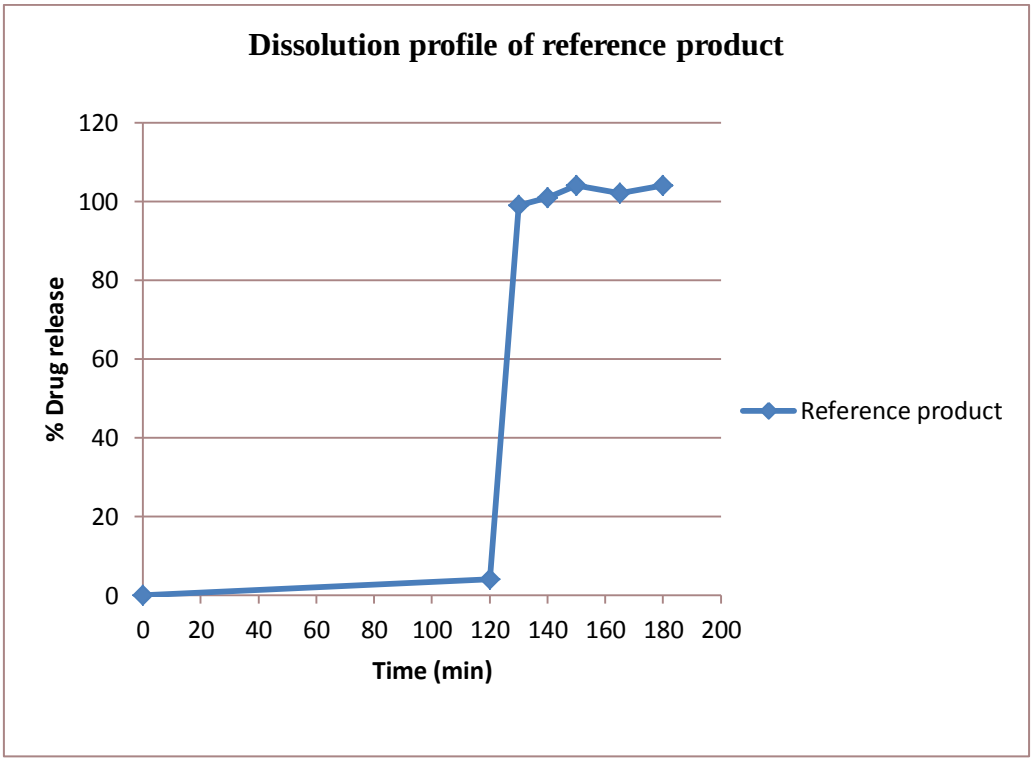

Figure 10: In-vitro dissolution profile of reference product

Observation and conclusion

Dissolution profile of reference in 750 ml 0.01 N HCl at 75 RPM for 120 min shows that dissolution is hindered in acidic medium whereas when the media is converted to 6.8 pH phosphate buffer along with 0.37% polysorbate 80, on same parameters the drug is dissolved. Hence the method has been selected as per OGD recommendation for further dissolution testing.

Table 15: In-vitro dissolution test of Reference product in pH 4.5 and pH 5.5 media.

Time (min)	% Drug dissolved	
	pH 4.5 acetate buffer	pH 5.5 phosphate buffer
10	2	3
15	2	3
30	3	3
45	3	3
60	3	3
90	3	3
120	3	3
150	3	3
180	3	3
Condition: USP Apparatus II, 75 RPM, Vol. 1000 ml		

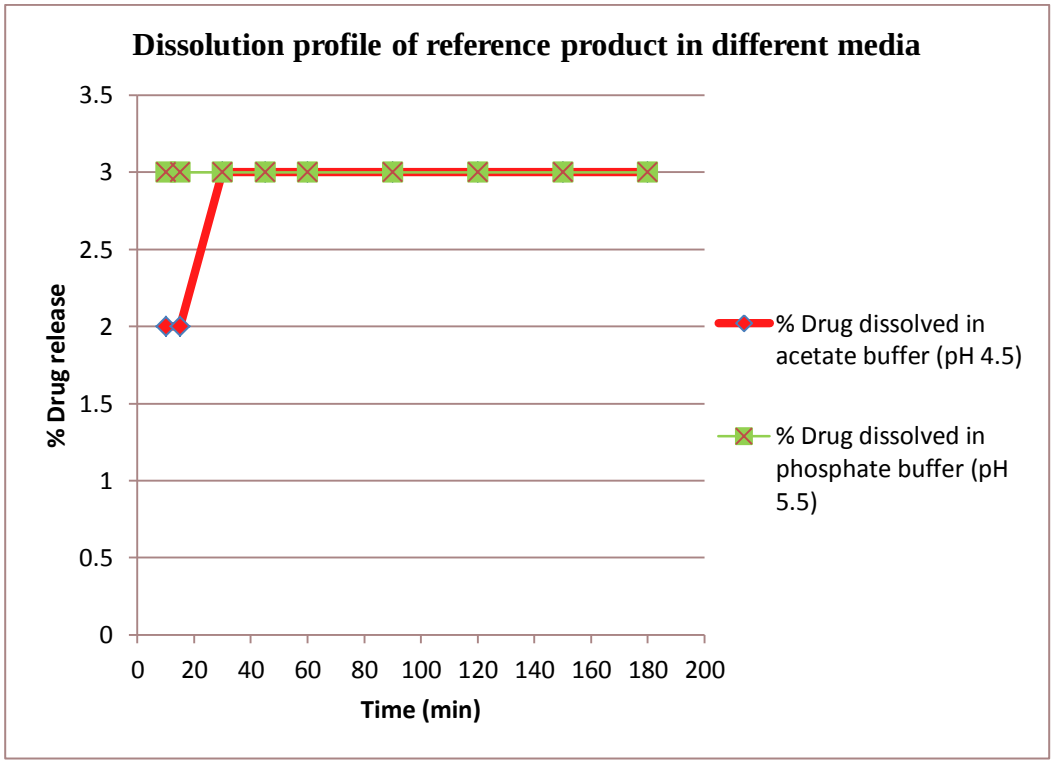

Figure 11: In-vitro dissolution of Drug from Reference tablet in pH 4.5 and pH 5.5 media.

Observation and conclusion:

The dissolution profile of reference product indicates that 2% drug dissolves in 15 min. in pH 4.5 acetate buffer and thereafter dissolves only 3% in pH 5.5 phosphate buffer till 180 min. Hence it can be said that the formulation is enteric release and it is formulated such that drug releases at intestinal pH i.e. pH 6.8.

Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA)

The Quality Target Product Profile of tablet is summarized in Table 16.

Table 16: Critical Quality Attributes (CQAs) of tablet formulation

QTPP Element	Target	Justification
Dosage form	Tablet	Pharmaceutical equivalence requirement: Dosage form same as that of Reference Product
Route of administration	Oral	Pharmaceutical equivalence requirement: Route of administration same as that of Reference Product

QTPP Element	Target		Justification
Container-closure system	High Density Polyethylene (HDPE) Bottles of with Child Resistance (CR) closure		Needed for patient safety as well as marketing requirement. Needed to ensure drug-product stability over the target shelf-life. Proposed packaging to ensure tablets integrity during shipping Closure to ensure child resistance, and tamper-proofing.
Stability	24 months shelf- life		Needed for efficacy and patient safety. Commercial/marketing requirement
Storage	Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].		To ensure drug-product stability over the shelf-life period Storage conditions in line with Reference Product
Drug product Quality Attributes	**Physical Attributes/Description**		
	Description	Film coated tablet	• Required for patient acceptability.
	Chemical attributes		
	Identification	Positive for selected drug substance	• Must comply with the identification test specific for the drug substance. • Needed for clinical effectiveness and patient-safety
	Assay	90.0% to 110.0% of label-claim	• To comply with compendial requirement. • Needed for clinical effectiveness.
	Uniformity of dosage units	To meet the requirement as per USP < 905>	To comply to specified compendial limits applicable per USP < 905>. Needed for clinical effectiveness
	Water content (%w/w)	To be monitored	Specification limits shall be assigned considering the manufacturing process, water content of the Drug substance and excipients,
	Degradation Products (% w/w)	Specified Degradation Product : NMT 0.2% Any Unspecified Degradation Product: NMT 0.2%	As per ICH Q3B (R2) threshold the limits for Specified and Unspecified Degradation Products

Drug-product quality attribute	Target	Critical/ Non-critical	Justification of Criticality
Physical Attributes			
Description	Film coated tablet	Non-Critical	Description is not directly linked to patient safety and clinical efficacy. Therefore, it is not critical. The target is selected considering patient acceptability, marketing requirements and reference product characterization.
Chemical Attributes			
Assay	90.0 to 110.0% of label-claim	Critical	Variability in drug-assay will affect patient safety and clinical efficacy. Formulations composition and/or process variables may affect the assay of the drug product, so this quality attribute is critical and will be evaluated during formulation and process development.
Uniformity of dosage units (UoD) (By content uniformity)	Meets the requirement of current USP <905>. Acceptance value: NMT 15	Critical	Content of Drug per tablet is less than 25%. Variability in content uniformity will affect assay which in turn will affect patient safety and clinical efficacy. Formulation and process variables may affect the uniformity of dosage unit of the drug product. Therefore this quality attribute will be evaluated throughout formulation and process development.
Dissolution	Should comply to dissolution criteria for delayed release dosage form	Critical	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables may affect the dissolution profile. This CQA is therefore critical and will be investigated throughout formulation and process development.
	Alcohol induced dose dumping: Comparable or lower drug release compared to the Reference product in 5% (v/v), 20% (v/v), and 40% (v/v) Alcohol USP apparatus -2, 50 RPM, 0.1N HCl dissolution medium.	Critical	Drug release in alcohol is critical to efficacy and patient safety. The target is set to ensure that alcohol stress conditions do not alter bioavailability of the developed product and introduce additional risks to the patient.

Drug-product quality attribute	Target	Critical / Non critical	Justification of Criticality
Degradation Products (%)	Specified Degradation Product : NMT 0.2% Any Unspecified Degradation Product: NMT 0.2%	Critical	Degradation products can impact safety and must be controlled based on compendial/ICH requirements or reference product characterization to limit patient exposure. Formulation and process variables can impact degradation products. Therefore, degradation products will be assessed during the formula finalization and process selection phase, and also monitored wherever necessary, during development.

INITIAL FORMULATION STRATEGY:

Different process approaches employed for formulation of drug: polymer solid dispersion were as below:

1. Top spray (Fluidized bed processor)
2. Bottom spray (Wurster coating)
3. Rotary evaporator
4. Rapid mixer granulator
5. Spray drying

The details of formula composition and process parameters of each approach are listed in following section.

5.1 TOP SPARY APPROACH

Table 17: Composition of formulation prepared by Top spray in fluid bed processor

S. No.	Ingredients	F01 (%w/w)	F02 (%w/w)
Intragranular			
1	Drug	16.39	16.39
2	Functional polymer	55.73	55.73
3	Dichloromethane	q.s.	q.s.
4	Methanol	q.s.	q.s.
5	Microcrystalline cellulose-PH 200	24.88	24.88
6	Croscarmellose Sodium	NA	1.00
Extragranular			
7	Hydroxypropyl Cellulose [EXF]	1	NA
8	Croscarmellose Sodium	1	1
9	Colloidal Silicon Dioxide	0.5	0.5
10	Magnesium stearate	0.5	0.5
11	TAB. wt (Total)	100	100

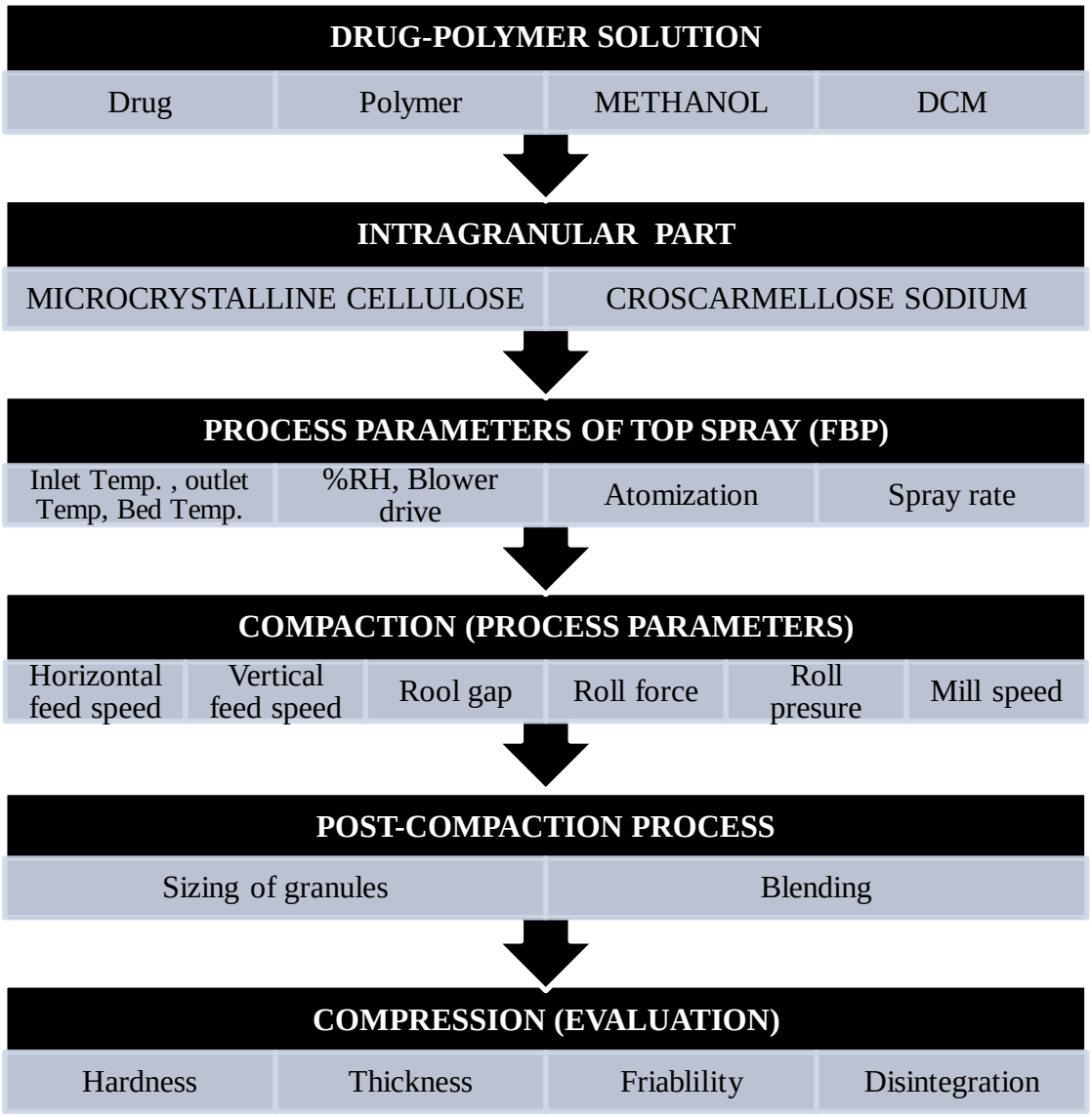

Figure 12: Schematic Process diagram followed for formulation development by top-spray approach

Table 18: Drug release from the different formulation prepared by Top spray approch in fluid bed processor

Time (min)	% Drug Release		
	R	F01	F02
0	**0**	**0**	**0**
120 (Acid stage)	4	2	28
130	99	19	99
140	101	24	99
150	104	27	100
165	102	59	100
180	104	67	98

R: Reference product

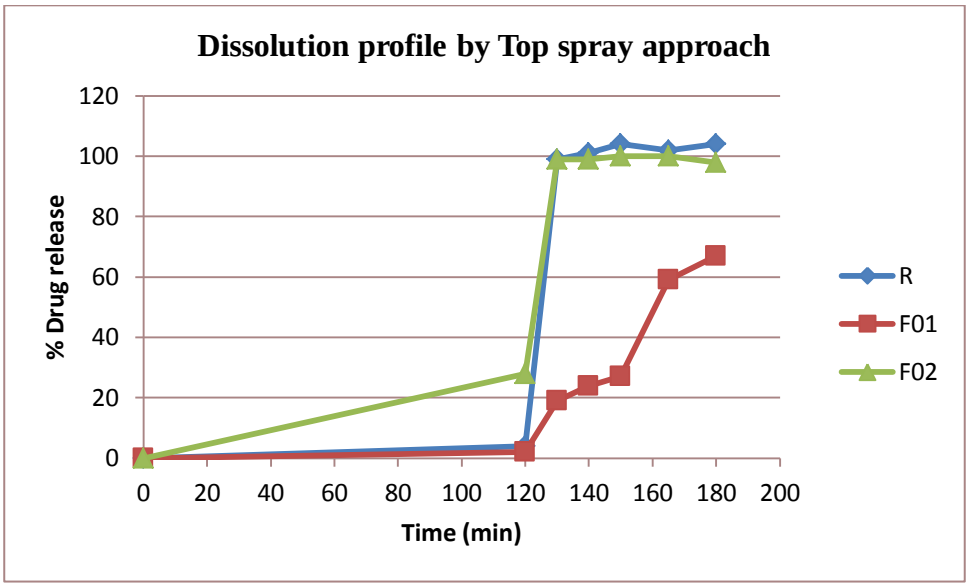

Figure 13: Comparison of drug release profile of different batches prepared top spraying in fluid bed processor.

Trial-F01 and F02: (Top spray approach)

- Top spray was performed. In trial no. F01, the dissolution profile of developed prototype was satisfactory in terms of acid resistance as less than 10% drug released was observed in 120min. However, complete drug release was not obtained in buffer stage.
- It was planned to fabricate a reproducible batch with similar qualitative composition in order to understand the effect on dissolution. It was also planned to add a super disintegrant in the intra-granular portion of the formulation. Therefore next trial was planned with above proposed change.
- In Batch F02, the dissolution was found to be complete in buffer stage. This may be due to the presence of intra-granular disintegrant addition in the formula composition which might have helped to achieve the faster and complete dissolution.
- However, in acid stage significantly higher dissolution (i.e., more than 25.0%) was observed.

  These results indicated that a suitable modification in formula or process is required.

Therefore next batch was prepared using Wurster –coating process. It was considered to coat the drug-polymer solution over MCC spheres with aim to increase overall surface area of drug substance which may help to achieve higher dissolution.

5.2 Formulation by Wurster coating approach

Table 19: Composition of prototype developed by Wurster Coating approach

S. No.	Ingredients	F03 (%w/w)
Intragranular		
1	Drug	16.39
2	Functional polymer	40.98
3	Dichloromethane	q.s.
4	Methanol	q.s.
5	microcrystalline cellulose (Celphere #70/140)	32.79
6	Croscarmellose Sodium	NA
Extragranular		
7	Functional polymer	NA
8	microcrystalline cellulose	6.84
9	Hydroxypropyl Cellulose [EXF]	1
10	Croscarmellose Sodium	1
11	Colloidal Silicon Dioxide	0.5
12	Magnesium stearate	0.5
13	TAB. wt (%)	100

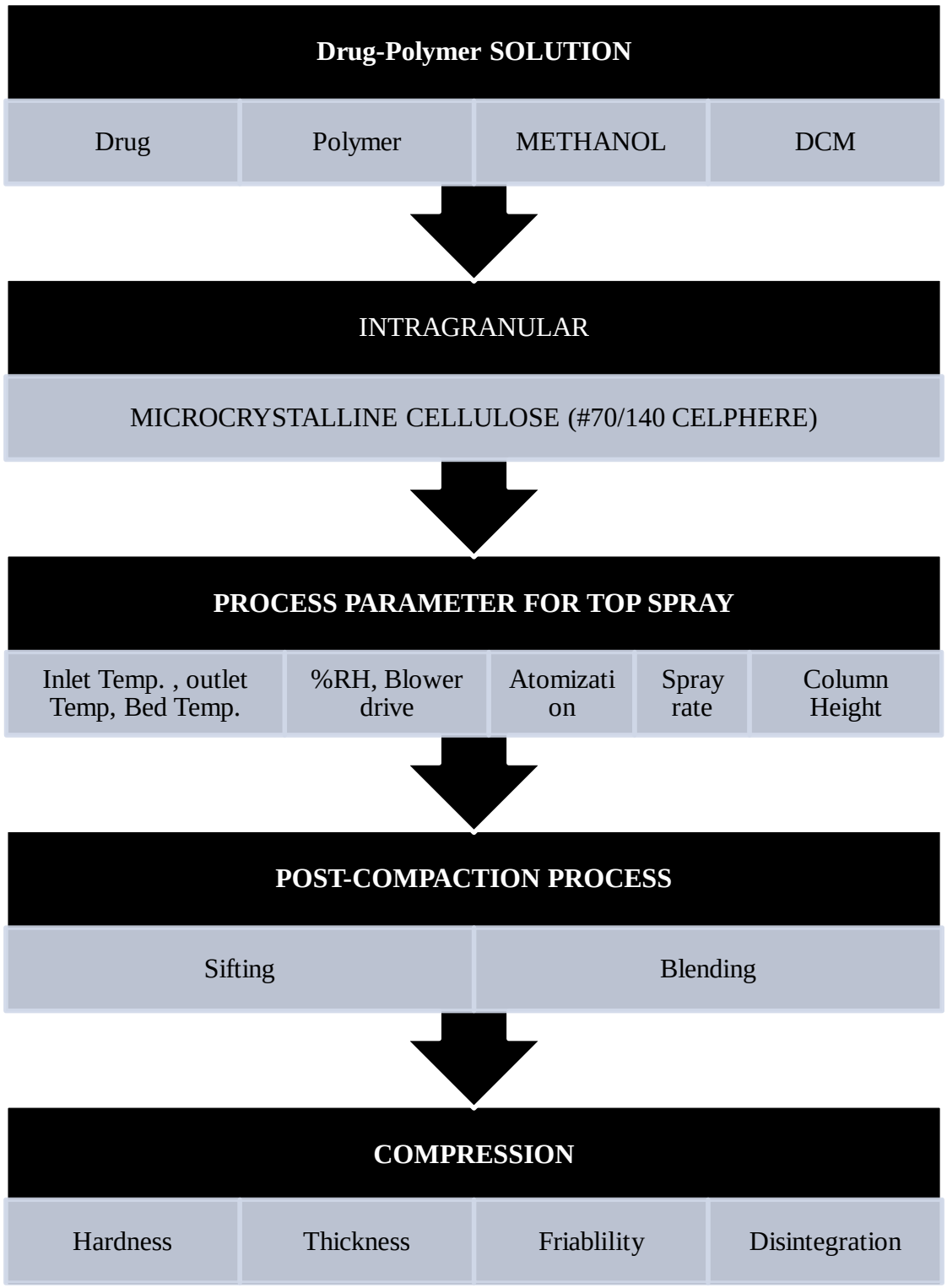

Figure 14: Schematic Process diagram followed for formulation development by top-spray approach

Table 20: Dissolution of prototype developed by Wurster Coating approach

Time (min)	% Drug Release	
	R	F03
0	**0**	**0**
120	4	2
130	99	5
140	101	5
150	104	6
165	102	8
180	104	10

R: Reference product

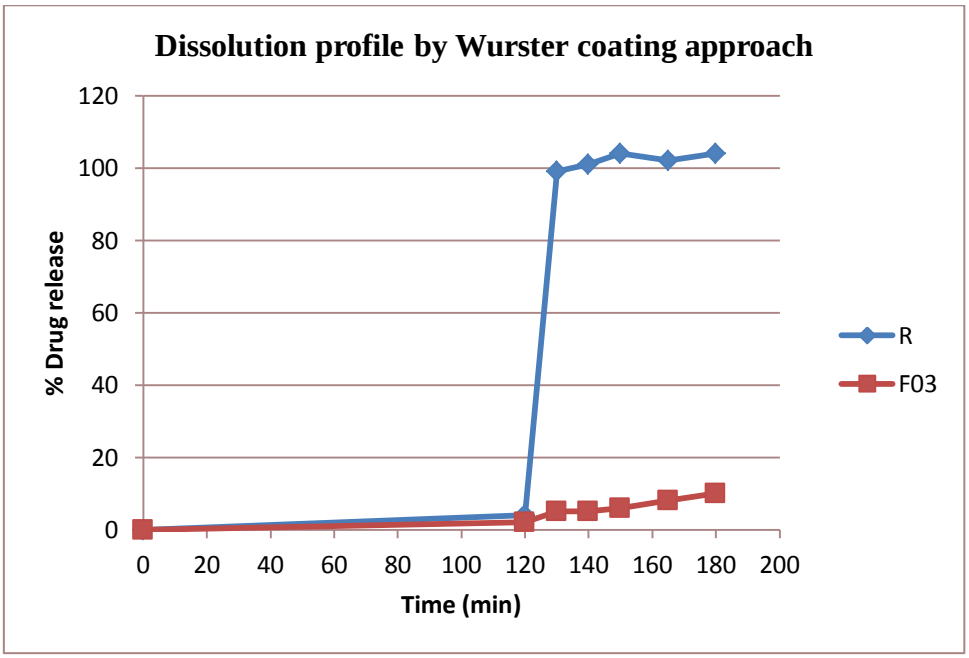

Figure 15: Comparison of drug release profile of prototype prepared by Wurster coating process

Trial-F03: (Bottom spray approach)

This trial was taken using the same solvent system (i.e., Acetone-methanol) for dissolving Polymer and drug. In this strategy the MCC spheres (Celphere #70/#140mesh; Mfd. by Aesahi-Kesahi) were loaded in Wurtser bowl, Drug-polymer solution was sprayed at suitable process parameters. Following critical observations were made during evaluation of this prototype.

- The drug-loaded spheres showed poor compressibility.
- As evident from the dissolution results summarized in Table 20, the Formulation F03 also failed to show the desired drug dissolution profile. Total drug released was only 10% including both acid and buffer stage.

Based on these results, this approach was not considered for further experimentation.

5.3 Prototype development by High shear mixing process using Rapid mixer granulator

Table 21: Composition of prototype developed by High shear mixer granulation approach

S. No.	Ingredients	F04 (%w/w)
Intragranular		
1	Drug	16.39
2	Functional polymer	36.07
3	Microcrystalline cellulose-PH 101	26.15
4	Croscarmellose Sodium	1.00
Binder solution		
5	Functional polymer	16.39
6	Dichloromethane	q.s.
7	Methanol	q.s.
Extragranular		
8	Hydroxypropyl Cellulose [EXF]	1.00
9	Croscarmellose Sodium	2.00
10	Colloidal Silicon Dioxide	0.50
11	Magnesium stearate	0.50
	TAB. wt (mg)	**100**

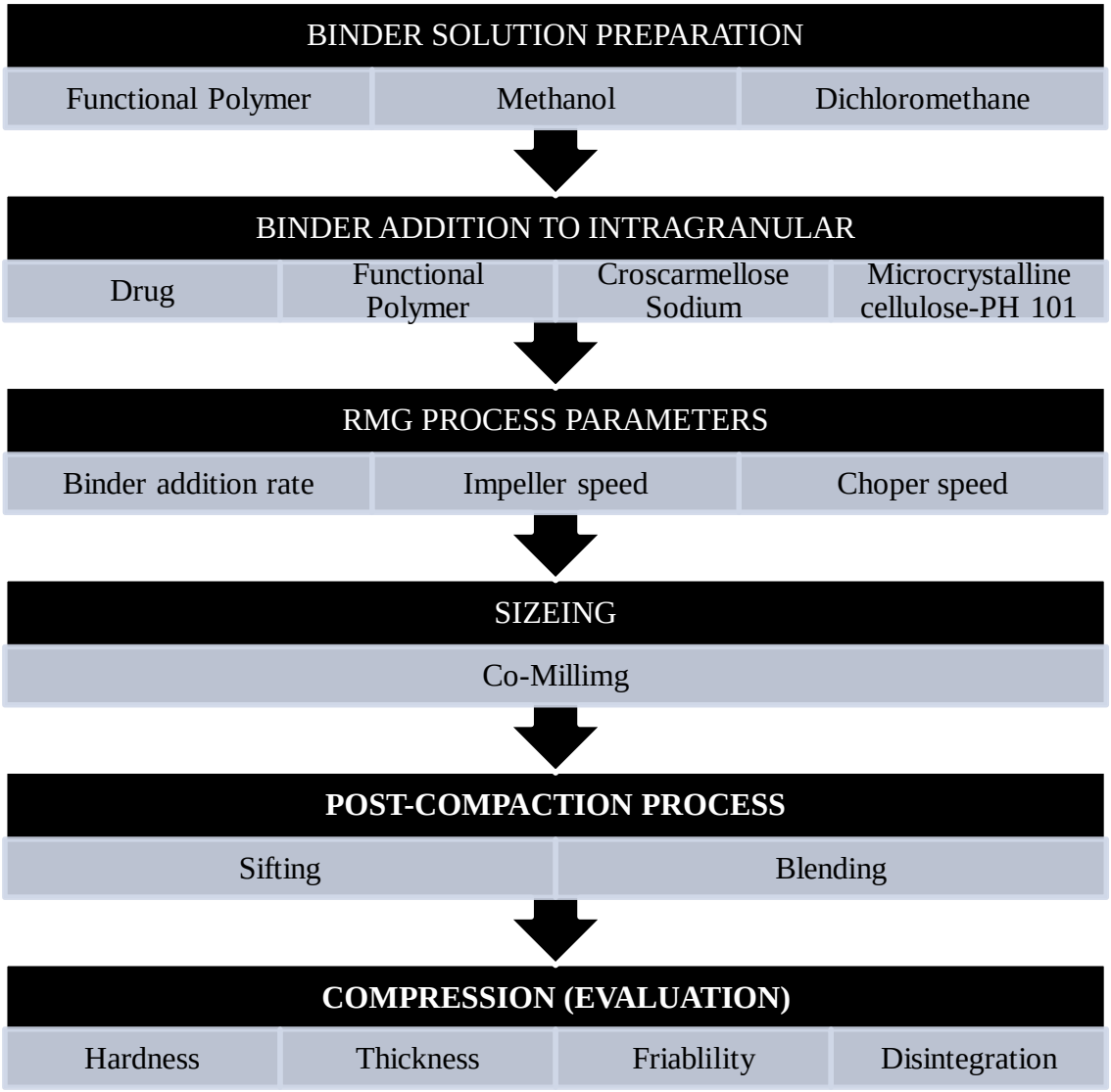

Figure 16: Schematic Process diagram followed for formulation development by High shear mixer granulation process

Table 22: Dissolution of prototype developed by High shear mixer granulation approach

Time (min)	% Drug Release	
	R	F04
0	**0**	**0**
120	4	13
130	99	34
140	101	41
150	104	45
165	102	45
180	104	46

R: Reference product

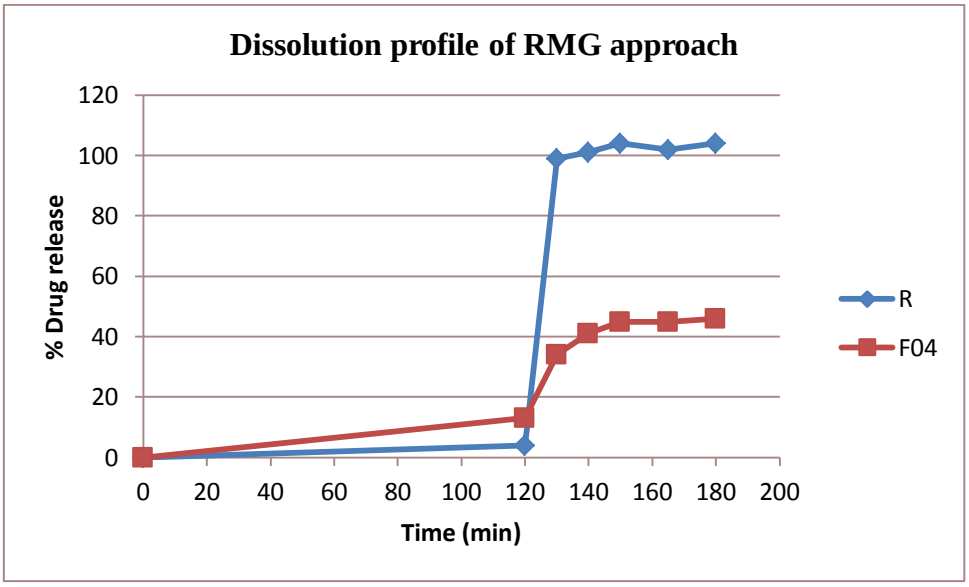

Figure 17: Comparison of drug release profile of prototype prepared by High shear mixer granulation process

Trial-F04: (Rapid Mixer Granulator)

- In this strategy the polymer was divided into two parts, in one part the polymer was used in the mixture of Polymer, Drug, MCC and CCS.
- The other part of polymer was used to prepare the binder solution in the Methanol-DCM solvent system.
- Multiple granulation approach was applied i.e. the granules was prepared using half portion of the binder solution. Followed by the drying in hot air dryer and milling to desired size and again using these granules for performing regranulation by using remainder of the binder solution.
- The final formulation did not match the dissolution profile of the reference product. The strategy was also not considered as the dissolution results were not satisfactory.

5.4 Prototype development by using rotary evaporation approach

Table 23: Formula composition of formulations prepared by Rotary evaporation approach

S. No.	Ingredients	F05 (%w/w)	F06 (%w/w)
Intragranular			
1	Drug	16.39	16.39
2	Functional polymer	49.18	55.73
3	Methanol	q.s.	q.s
4	Dichloromethane	q.s	q.s
Extragranular			
5	Microcrystalline cellulose	31.43	24.88
6	Hydroxypropyl Cellulose [EXF]	NA	NA
7	Croscarmellose Sodium	2.0	2.0
8	Colloidal Silicon Dioxide	0.50	0.50
9	Magnesium stearate	0.50	0.50
10	**TAB. wt (%)**	**100**	**100**

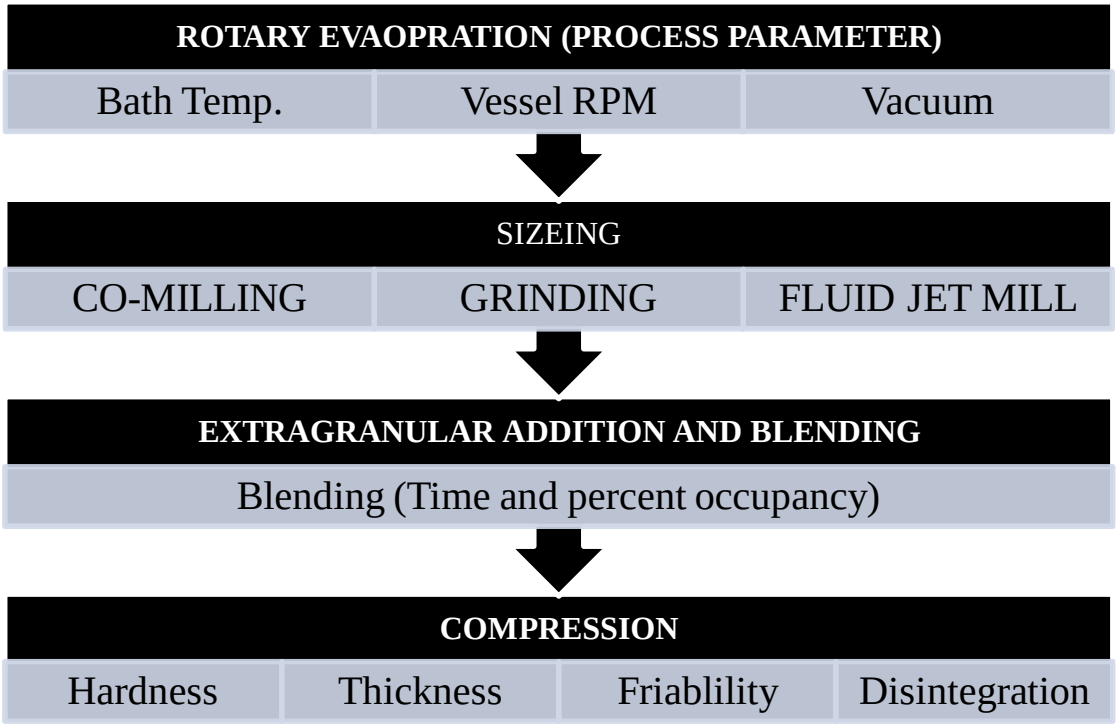

Figure 18: Schematic Process diagram followed for formulation development by rotary evaporation process

Table 24: Dissolution of prototype developed by rotary evaporation approach

Time (min)	% Drug Release		
	R	F05	F06
0	**0**	**0**	**0**
120	4	13	3
130	99	34	42
140	101	41	50
150	104	45	54
165	102	45	56
180	104	46	57

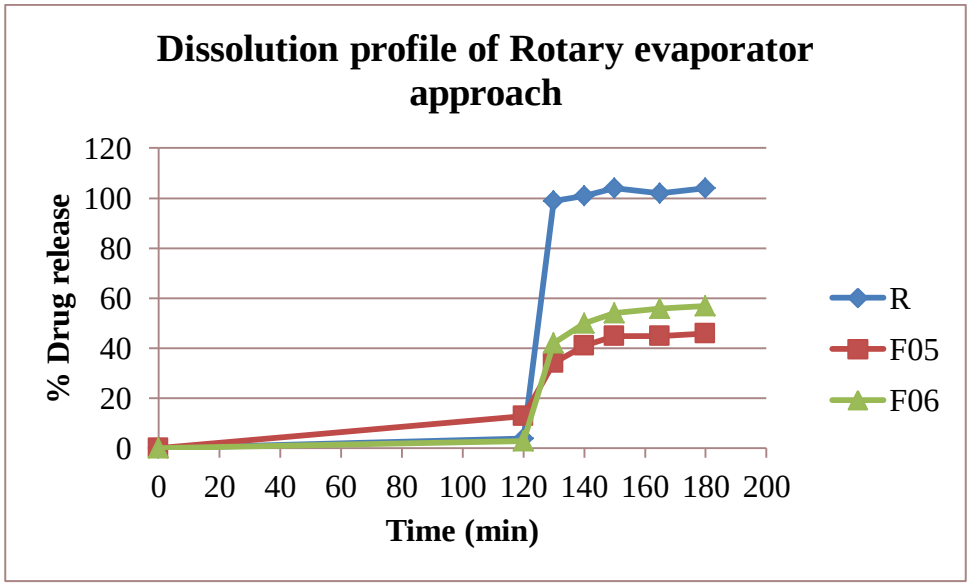

Figure 19: Comparison of drug release profile of reference product with two formulation prepared by rotary evaporation process

Trial-F05: (Rotary evaporator)

- In this technique of preparing solid dispersion, the Drug-Polymer was used in ratio of 1:3 in DCM-methanol solvent system. The removal of solvent was done by giving heat to the system and applying vacuum for faster removal of the solvent.
- The product was scraped from the vessel and collected for further processing.
- The formulation was able to restrict the dissolution of Drug in acidic medium (13% release) but was unable to show immediate release in buffer medium.

- This implies that a higher quantity of polymer should be used so that its solubility enhancing property can be used to accomplish the desired goal.

Trial-F06: (Rotary evaporation approach)

- In this trial, drug-polymer solid dispersion was prepared by dissolving Drug-Polymer in the ratio of 1:3.4 in DCM-methanol organic solvent system. The removal of solvent mixture was done by rotary evaporation using Buchi rotary evaporator at temperature 45±5°C, under vacuum.
- The product was scraped from the vessel of the round bottom flask and collected for further processing.
- As evident from the dissolution results shown in Table 24, the formulation was able to restrict the dissolution of Drug in acidic medium. The dissolution in acid stage was as per the target i.e., below 10.0% and also almost 90% drug release was observed in buffer stage. Results indicated that solid dispersion formation by rotary evaporation approach yielded satisfactory results. However, it was planned to also evaluate spray-drying approach.

5.5 Prototype development by spray drying approach

Table 25: Formula composition of formulations prepared by spray drying approach

SPRAY DRYING			
S. No.	Ingredients	F07 (%w/w)	F08 (%w/w)
Intragranular			
1	Drug	16.39	16.39
2	Functional polymer	40.98	55.73
3	Methanol	q.s.	q.s
4	Dichloromethane	q.s	q.s
Extragranular			
5	Microcrystalline cellulose	37.62	22.87
6	Hydroxypropyl Cellulose [EXF]	1	1
7	Croscarmellose Sodium	3.0	3.0
8	Colloidal Silicon Dioxide	0.50	0.50
9	Magnesium stearate	0.50	0.50
10	**TAB. wt (mg)**	**100**	**100**

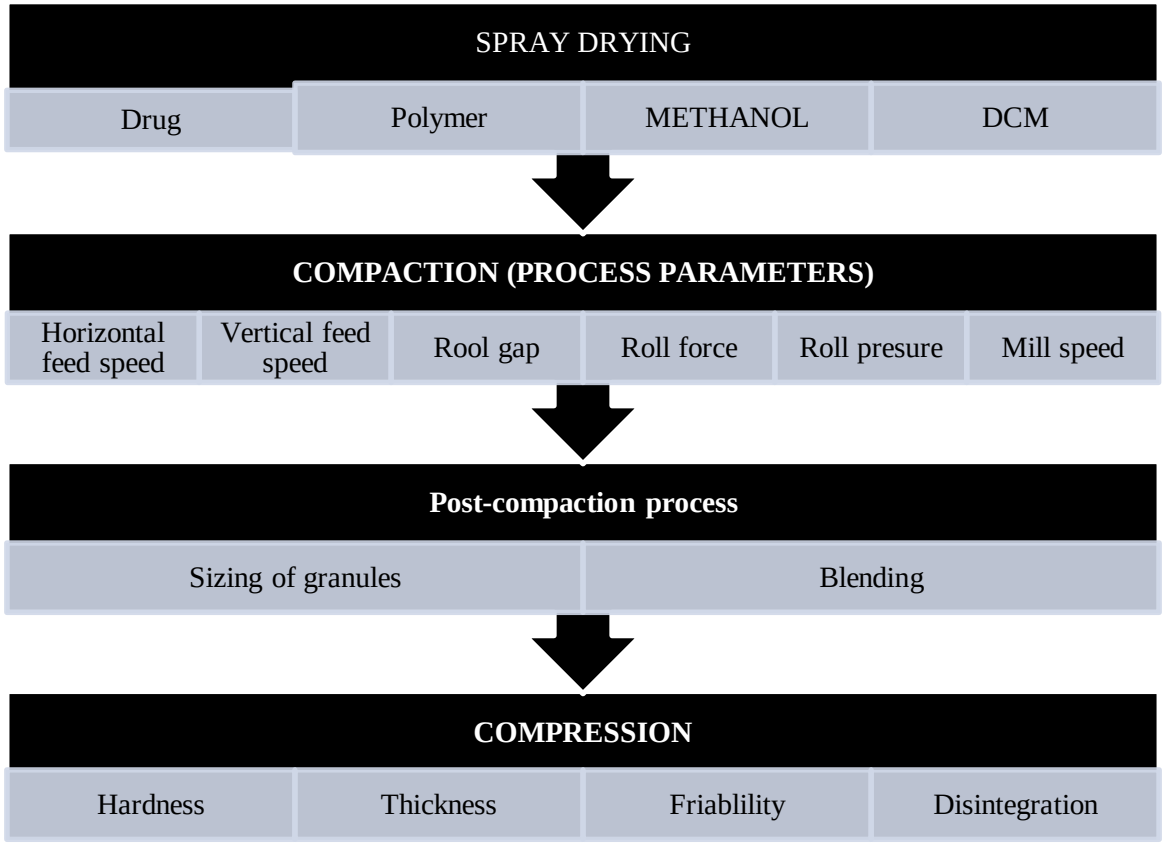

Figure 20: Schematic Process diagram followed for formulation development by rotary evaporation process

Table 26: Dissolution of prototype developed by spray drying approach

Time (min)	R	F07	F08
0	0	0	0
120	4	37	16
130	99	93	95
140	101	94	99
150	104	94	98
165	102	94	100
180	104	93	100

R: Reference product

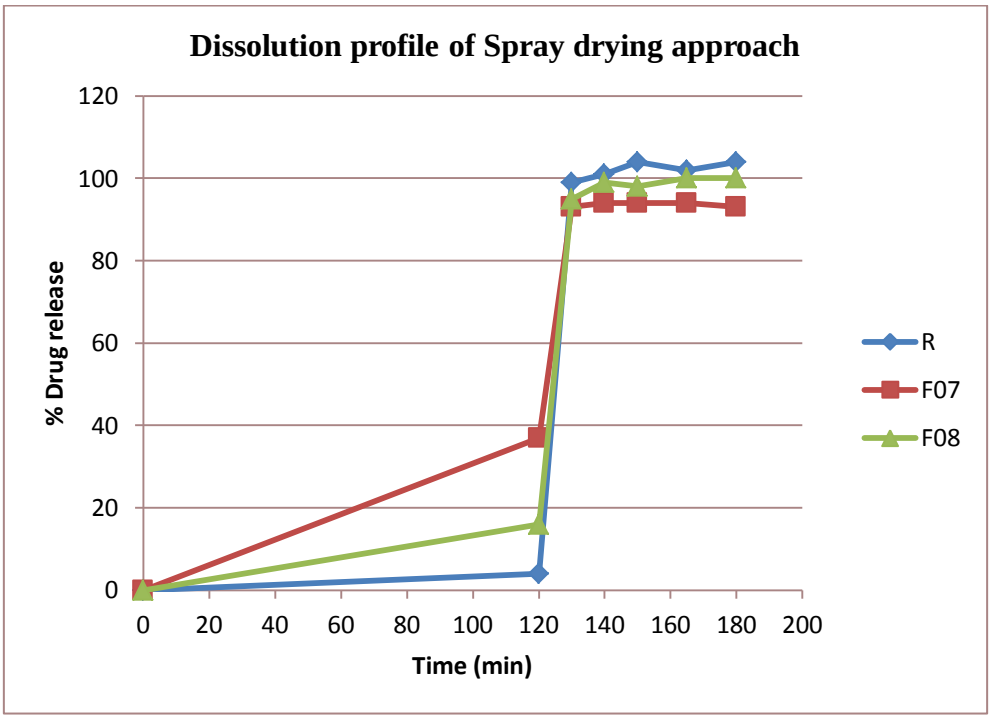

Figure 21: Comparison of drug release profile of reference product and prototype formulated with spray drying formulation

Trial-F07: (Spray drying)

- In this technique same solvent system was used as in previous techniques.
- The ratio of Drug: Polymer was 1:2.5
- In this approach the process variables which were studied are spray rate, inlet temperature, outlet temperature, aspiration and atomization.
- The formulation prepared by this approach was successful in showing immediate release in buffer stage but was not much effective in restricting the drug release in the acid stage.
- This implies that an optimum concentration of polymer should be used and an optimum Drug-Polymer ratio should be selected.

Trial-F08: (Spray drying)

- In this trial, slight modification in the amount of polymer was carried out as compared to previous formulation (i.e., Batch F07) which was prepared by using spray drying.
- The solvent system employed for this batch was same as that used in batch F017.
- Ratio of Drug: Polymer was increased from 1:3.2 to 1:3.4.
- The process variables which were studied include spray rate, inlet temperature, outlet temperature, aspiration and atomization.
- Using spray dried material; tablets were compressed and further coated to achieve retardation of dissolution in acid stage.
- The compressed tablets were coated with selected polymer dissolved in organic solvent mixture to a weight build-up of 8.0% and evaluated for dissolution release profile as shown in Table 37. Dissolution profile of batch of F019B was found to be satisfactory.
- Overall, results suggested formulation prepared by spray drying approach was successful in showing immediate release in buffer stage and was also able to restrict the Drug release in the acidic medium.

5.6 SUMMARY OF TRIALS

Table 27: Comparative formula composition of different formulation approaches

S. No.	Ingredient	Formula composition (%w/w)							
		Top spray		Wurster	RMG	Rotary evaporator		Spray drying	
		F01	F02	F03	F04	F05	F06	F07	F08
Intra-granular									
1	Drug	16.39	16.39	16.39	16.39	16.39	16.39	16.39	16.39
2	Functional polymer	55.73	55.73	40.98	36.07	49.18	55.73	40.98	55.73
3	Methanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
4	Dichloromethane	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
5	Microcrystalline cellulose	24.88	24.88	32.79	26.15	NA	NA	NA	NA
6	Croscarmellose Sodium	NA	1.00	NA	1	NA	NA	NA	NA
Extra-granular									
7	Functional polymer	NA	NA	NA	16.39	NA	NA	NA	NA
8	Microcrystalline cellulose	NA	NA	6.84	NA	31.43	24.88	37.62	22.87
9	Hydroxypropyl Cellulose [EXF]	1	NA	1	1	NA	NA	1	1
10	Croscarmellose Sodium	1	1	1	2	2	2	3	3
11	Colloidal Silicon Dioxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
12	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
TABLET WEIGHT		**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Table 28: Comparative drug release using different formulation approaches

Stage	% Drug Release									
	Time point (min)	Reference product	Top spray		Wurster	RMG	Rotary evaporator		Spray drying	
			F01	F02	F03	F04	F05	F06	F07	F08
Acid Stage	0	0	0	0	0	0	**0**	**0**	**0**	0
	120	**4**	**2**	**28**	**2**	**13**	**3**	**5**	**3**	**16**
Buffer Stage	130	99	19	99	5	34	42	68	45	95
	140	101	24	99	5	41	50	84	67	99
	150	104	27	100	6	45	54	89	79	98
	165	102	59	100	8	45	56	91	84	100
	180	104	67	98	10	46	57	92	85	100

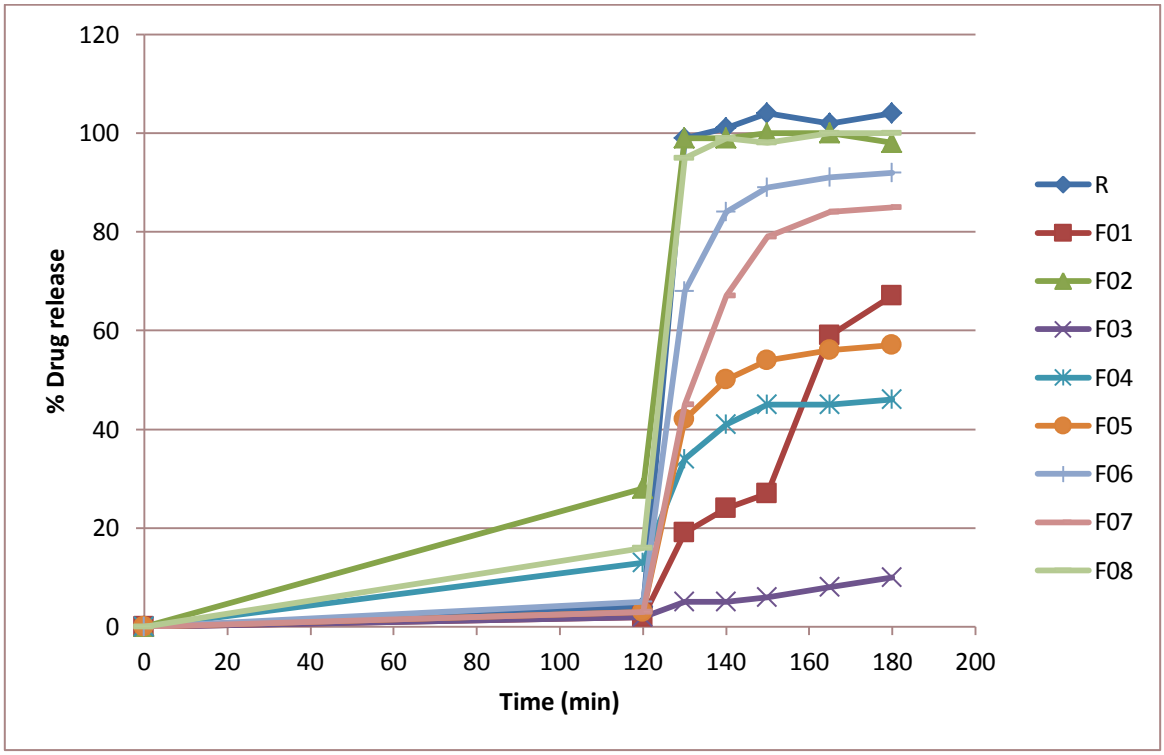

Figure 22: Comparison of drug release profile of different formulation with that of reference product

Functional coating

The formulation F08 has shown convincing drug release profile compared to other batches prepared. It has also shown quite similar drug release profile as that reference product, but still drug release in acid stage was a bit more. So a coating with functional polymer was done.

Table 29: Dissolution of coated tablets of prototype developed by spray drying approach

Time (min)	Formulation		
	R	F08A	F08B
0	**0**	**0**	**0**
120	4	3	2
130	99	49	94
140	101	86	98
150	104	99	101
165	102	109	103
180	104	109	107

- **R: Reference product**

Trial F08A:

- Polymer "A" solution was prepared and plasticizer was also used.
- The drug release was satisfactory in acidic stage but the release profile was not satisfactory in buffer stage. So a different polymer was used.

Trial F08A:

- Polymer "B" solution was prepared and similar plasticizer was used as in formulation F08A..
- The drug release was satisfactory both in acidic stage and also in buffer stage. It has shown similar drug release profile as that of reference product. Hence it was selected as optimized batch.

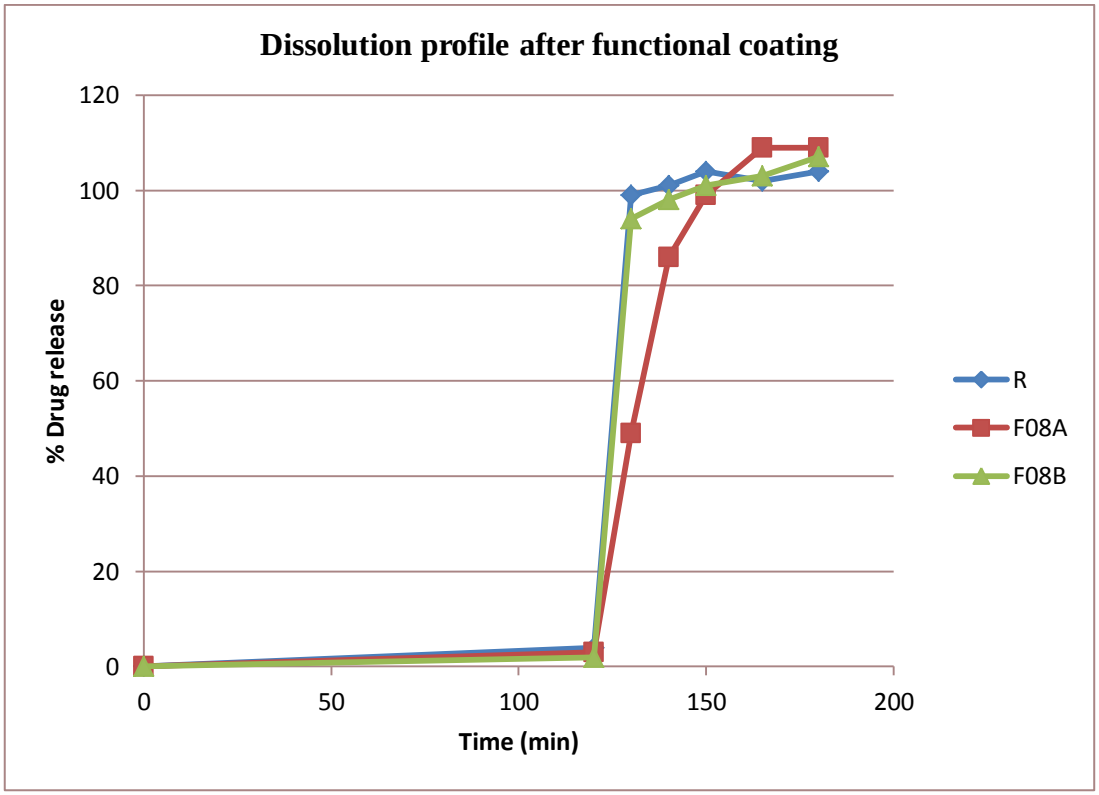

Figure 23: Comparison of drug release profile of reference product and prototype formulate after functional coating.

6.0 Conclusion

Since Drug has low solubility, and reference product has negligible drug release in acidic medium, faster release in buffer, different technologies are used to formulate and evaluate formulation. Solid dispersion technology with drug and selected functional polymer was attempted. It retards dissolution in acid medium and increases solubility in buffer stage. Different formulation techniques including FBP top spray, rotatory evaporator, Wurster coating (FBP bottom spray) and spray drying were evaluated. Drug-polymer solution was sprayed directly or on a solid material to produce a mass for compression. Results were satisfactory with spray drying and rotary evaporation technique. High-shear granulation using RMG was also performed, so that drug remains intact within the polymer but the results with this strategy were not promising. Effect of Drug: polymer ratio was evaluated. It was observed that a certain minimum concentration of polymer (Drug: Polymer – 1:3.4) is required to achieve effective solid dispersion formation and solubility enhancement. Further, in one of the prototypes developed, role of enteric coating was also evaluated by using two different functional polymers to achieve retardation of drug release in acidic medium. Tablets coated with both polymers exhibited similar dissolution results and were comparable to Reference product. Solid-dispersion formulations of selected drug-candidate with Spray drying techniques was found to be best as compared to other techniques, and the batch F08B which was coated with a suitable functional polymer showed similar drug release profile as that of reference product hence it was selected as the optimized batch.

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