International Journal of Advances in Pharmaceutical Analysis
IJAPA Vol. 5 Issue 4 (2015) 93-110

Comparative evaluation for effect of moisture activated dry granulation in tablet with conventional technique

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Abstract

The purpose of undertaken project was to develop Moisture activated dry granulation (MADG) process for tablet formulation, to overcome the difficulties experienced with conventional wet granulation in terms drying, milling and substances sensitivity towards heat & moisture. For this Metoprolol succinate is used as model drug and the granulation is done by MADG and conventional wet granulation technique. The granules were prepared using spressB8 18 and prosolv SMCC 90 as an adsorbent. They have an objective of adsorbing moisture from the powder blend and redistributing it, thus eliminating one step of drying. In trial batches the effects of varying concentration of both adsorbents were explored. Granules were evaluated for parameters such as amount of fines, drying time, bulk density, compressibility, angle of repose etc. The study indicated that the granules retained their structure in comparison with the conventional process with respect to all the physicochemical parameters. In order to obtain acceptable product several trials were conducted and finally factorial batches were prepared using spressB8 18 only. The 9 formulation were prepared by varying concentration of spressb8 18 and water. The prepared granules were compressed in to tablets & they are evaluated for various pharmacopoeial evaluations like weight variation, hardness, disintegration time, friability and *in-vitro* dissolution. Lastly, the comparison is done between Final optimized formulation & conventional one.

Keywords: Moisture activated dry granulation, Adsorbents, SpressB8 18 and Prosolv SMCC 90.

1. Introduction

Oral drug delivery is the most desirable and preferred method for drug administration and consider as First Avenue investigated in drug discovery and development. Among all dosage forms, tablet is the most popular dosage form. About half of all prescriptions are dispensed in compressed tablets. Since many years a comprehensive research is being done to study processes used to manufacture tablets. The tablets are prepared by following method. [1]

A. Direct Compression

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required. Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression, thus offering advantage particularly in terms of speedy production, as it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability. [2]

Advantages:

1) Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.
2) The most important advantage of direct compression is that it is an economical process. Reduced processing time, reduced labor costs, fewer manufacturing steps, and less number of equipments is required, less process validation, reduced consumption of power.
3) Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API.
4) Particle size uniformity.
5) Prime particle dissolution.
6) In case of directly compressed tablets after disintegration, each primary drug particle is liberated. While in the case of tablets prepared by compression of granules, small drug particles with a larger surface area adhere together into larger agglomerates; thus decreasing the surface area available for dissolution. [2]

Disadvantages:

Excipients Related

1) Problems in the uniform distribution of low dose drugs.
2) High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression for example, Aluminum Hydroxide, Magnesium Hydroxide.
3) The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flowability.
4) Many active ingredients are not compressible either in crystalline or amorphous forms. [2]

Process Related

1) Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.
2) In some cases require greater sophistication in blending and compression equipments.
3) Direct compression equipments are expensive. [2]

B. Dry Granulation

Dry granulation involves granule formation without using liquid solution as the product may be sensitive to moisture and heat. It is the least desirable of all the methods of granulation. In this process dry powder particles may be brought together mechanically under low pressure by compression into slugs or by roller compression to obtained flakes.[2] The compacts so-formed are broken up gently to produce granules (agglomerates).Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may need to be added to the formulation to facilitate the formation of granules. At last powdered lubricants are added. [3]

Advantages

The main advantages of dry granulation or slugging are that it uses less equipments and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step

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required for wet granulation. Slugging can be used for advantages in the following situations:

i) For moisture sensitive material.

ii) For heat sensitive material.

iii) For improved disintegration since powder particles are not bonded together by a binder. [3]

Disadvantages

i) It requires a specialized heavy duty tablet press to form slug

ii) It does not permit uniform colour distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.

iii) The process tends to create more dust than wet granulation, increasing the potential contamination. [3]

Two main dry granulation processes

1 Slugging process

Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly.Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.[2]

2 Roller compaction

The compaction of powder by means of pressure roll can also be accomplished by a machine called chilosonator. Unlike tablet machine, the chilosonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules. [2]

C. Wet Granulation

WG technique is receiving great significance and widely used by pharmaceutical industry, because direct compression method is not the most suitable technique for many active substances that are in high dosages or in fine powder form, also the moisture content of drugs, excipients combined with the drugs to manufacture a final dosage form (i.e compressed tablets), and/or processing manipulations involving moisture may have a significant impact on wide range of chemical and physical properties of the finished product.[4]

WG involves addition of a liquid solution (with or without binder) to powders, to form a wet mass or it forms granules by adding the powder together with an adhesive, instead of by compaction. The wet mass is dried & then sized to obtained granules. The liquid added binds the moist powder particles by a combination of capillary and viscous forces in the wet state. More permanent bonds are formed during subsequent drying which leads to the formation of agglomerates. [5] There are few drawbacks associated with the wet granulation technique is that the process is expensive because of labor, space, time, special equipment and energy requirement, multiple processing steps involved in the process add complexity which makes validation and control difficult, loss of material during various stages of processing and not suitable for moisture sensitive and thermo labile drugs. An inherent limitation of wet granulation is that any incompatibility between formulation components is aggrevated. [2]

I. Hydrate formation

For example, theophylline anhydrous during high shear wet granulation transfers to theophylline monohydrate. The midpoint conversion occurs in three minutes after the binder solution is added. For online monitoring of the transformation from one form to another, Raman spectroscopy is most widely used. [5]

II. Polymorphic transformation

The drying phase of wet granulation plays a vital role for conversion of one form to another.

For example, glycine which exist in three polymorphs that is a, β, g . g is the most stable form and a is the metastable form. The stable Glycine polymorph (g) converts to metastable form (a) when wet granulated with microcrystalline cellulose. [5]

All of the Traditional or conventional granulation processes are excellent ways to produce quality granules for tableting or capsule filling, but they require significant production time and energy, so efforts have been made to simplify processes, reduce processing time, increase efficiency, and improve drug content uniformity. [3]

Ullah et al. in 1987 described a modified wet granulation process that was named as moisture activated dry granulation (MADG), where granules are formed by moisture and heat is not used for drying of granules. During this process, the generation of moist agglomerates is followed by the stepwise addition and blending of common pharmaceutical ingredients that absorb and distribute the moisture, which results in a uniform, free-flowing and compactable granulation. In MADG process, the whole process is considerably shorter than a typical wet granulation. [2]

Moisture Activated Dry Granulation: A standard granulation approach

1. Background of MADG Process

The present article relates to a moisture-activated granulation process for manufacturing pharmaceutical compositions, in particular solid dosage forms of active substances which are prone to chemical degradation and/or physical phase transitions upon contact with heat and water or aqueous liquids such as those used during conventional wet granulation processes.[6]

Moisture Activated Dry Granulation (MADG) was developed in response to the difficulties experienced with wet granulation, in terms of endpoint, drying and milling. Wet granulation process endpoint is very sensitive to granulation time and shear. The wet granules need to be dried to a narrow range of moisture contents, which is difficult. The dried granules need to be milled, but the milled granules often have either too many fines or too many coarse particles (or both) - an undesirable bimodal distribution. [7]

2. Criteria behind the Granule formation in MADG process

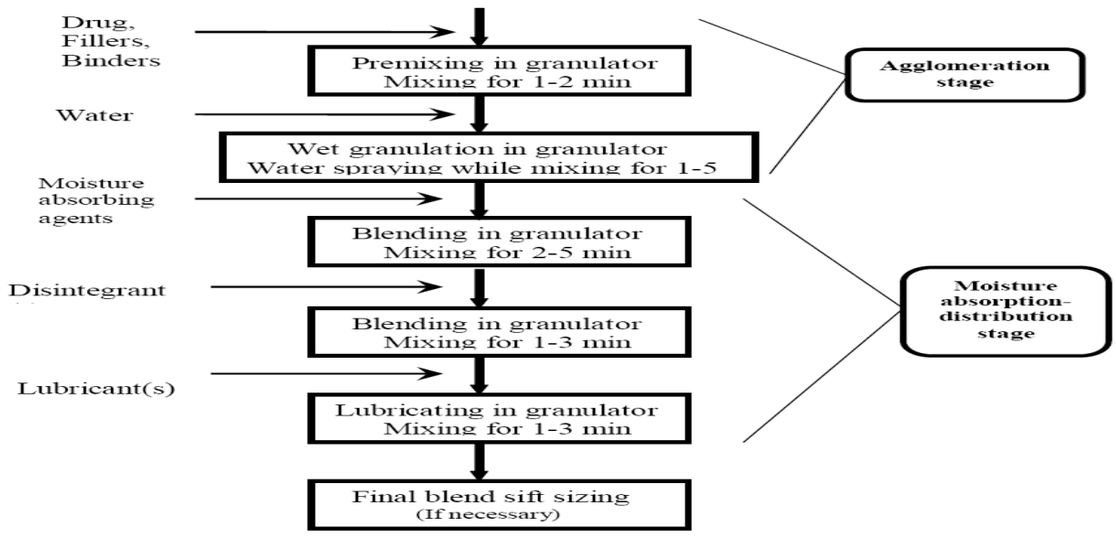
The granule formation mechanism in MADG is the same as in conventional wet granulation. In both cases, it is a process of powder particle size enlargement, often in the presence of water and binders, through wet massing and kneading. The main differences between the two are the amount of granulating liquid used and the level of agglomeration achieved. In conventional wet granulation, substantially more water is utilized to create larger and wetter granules. This is then followed by heat drying to remove the excess water and milling to reduce the granule size. [8]

In MADG, only a small amount of water is used to create agglomeration, followed by moisture distribution and absorption. Neither heat drying nor milling is required. Because the amount of water used in MADG is small (usually only 1–4% of the entire formulation), it is important that the water is delivered accurately and distributed uniformly during the agglomeration stage this makes the selection of a spray system that provides accurate delivery and a well-defined spray pattern very important.[8]

3. The Principle of MADG process

The Moisture Activated Dry Granulation involves two major stages

1. Agglomeration
2. Moisture distribution And Absorption Stage. [9,11]



Moisture- Activated Dry Granulation – Formulation Development

A. Agglomeration

In this stage, all or part of the drug is mixed with filler(s) and an agglomerating binder to obtain a uniform mixture. During mixing, a small amount of water (1–4%) is sprayed onto the powder blend; water droplets hydrate the dry binder and create tacky nuclei or tacky wet mass. The binder functions as the drug and excipients move in the circular motion caused by the mixer impellers or blades.Dry powder particles adhere to the wet nuclei or wet tacky mass to create moist agglomerates the resulting agglomerates are small and spherical because the amount of water used in the MADG process is much lower than that in conventional wet granulation. The agglomerates therefore cannot grow into large, wet lumps. The particle size of the agglomerates generally is in the range of 150–500 µm. [9]

B. Moisture-Distribution and Absorption Stage

In this stage, moisture absorbents are added as mixing continues. When these agents come into contact with the moist agglomerates, they pick up moisture from the agglomerates and redistribute moisture within the mixture. The entire mixture thus becomes relatively dry. This process results in a granulation with uniform particle size distribution. [9]

Advantages

1) Applicable to more than 90% of the granulation needs for pharmaceutical, food and nutritional industry.
2) Short processing time.
3) It utilizes very little granulating fluid, so decreases in drying time also produces granules with excellent flowability.
4) Very few variables, resulting in less need for expensive PAT technology.
5) Applicable to number of formulation, including low and high drug load formulation, polymer matrix type controlled release formulations, soluble and insoluble type drug formulation.
6) Single production equipment (high shear granulator) hence Suitable for continuous processing.
7) It uses very little energy, therefore it is green process.
8) Lower tablet capping.
9) Additionally, because of the necessary excipients required for MADG are already commonly used by the pharma industry so there is no conceivable regulatory concern.
10) It creates relatively small granules of narrow particle-size distribution with good flowability. The MADG-based granulations also tend to have good compactibility and weight control during tablet compression.
11) The potential for segregation is eliminated for two main reasons. First, the agglomeration stage constitutes 70–90% of the entire formulation in most cases. Second, the excipients added in the moisture-absorption stage often have a particle size similar to that of the agglomerates.
12) It is one pot process.
13) Reproducible, scalable & requires No equipment change
14) The MADG process is also amenable to scale-up with few or no risks. For example, a large-scale batch typically results in a uniform water distribution, which is desirable and beneficial.
15) The minimalist aspect of the process is manifest in the fact that the process involves few pieces of equipment and manufacturing steps. The net processing time of the MADG process is short, also offers energy savings and no additional requirements for drying, extra material transfer, milling, and separate blending exist.
16) These advantages make the MADG process a good candidate for the application of the US Food and Drug Administration's quality by design (QbD) philosophy. Because the process does not need granulation drying or milling steps, it is a green process that has a great potential to be developed into a continuous process. [10,11]

Disadvantages:

1) Extremely Moisture sensitive and high moisture absorbing APIs are poor candidates.
2) Formulations with high drug loading are difficult to develop. [10,11]

4. Important considerations in MADG process

1. Assessment of API Wettability

Drug solubility, particle-size distribution, and desired drug loading in the formulation are the primary factors to be considered for an MADG-based development. In general, a great amount of agglomerating binder and water are needed to create the agglomerates when a high drug load is desired for a drug with low solubility and small particle size. The converse is also true. Less

agglomerating binder and water is required if the drug is water-soluble, the particle size is not small (e.g., > 10 μm), and the drug loading is low (e.g., < 25%). Self-granulating drugs sometimes do not require any binder and need less water to granulate. Drug attributes such as Wettability and agglomeration characteristics should be determined experimentally if they are not already known. [11]

2. Moisture in formulation

The amount of water used in the MADG process is part of the formula composition. This amount is a fixed value in the formula and is determined during formulation development. For example, if 2.0% (w/w) water is used, the rest of the ingredients should make up the 98.0% (w/w) of the formula. Because the MADG process does not include a heat-drying step, the water added would not be intentionally removed from the formulation. Because moisture is added but not removed in the MADG process.[11]

3. **Required equipment for MADG**

MADG only requires two pieces of equipment:

A. An appropriate granulator.

B. An airless spray system.

A. Granulator

The granulator can be a planetary or high-shear granulator, but the blades should be at the bottom (either top or bottom driven) and not exposed. This is necessary because the amount of water used is very small and added on top of the powder bed by a fine spray. If the blades were exposed, the water could hit the blades and cause loss of water, possibly creating wet lumps and nonuniform granulation. The granulator should not have dead spots or spots where material could stick. A chopper in the granulator is also useful.

B. Water delivery system/airless spray system

The preferred mechanism to deliver water spray consistently would be an airless spray system, which enables the water to be directed onto the powder bed in a high-shear granulator. Any airless spray nozzle with a gear pump or pressure vessel, where the spray pattern can be reproduced and the exact amount of water delivered, would be adequate. Spray nozzles with an orifice of 0.1 mm or 0.15 mm can be attached to a syringe to deliver a low (5–10 mL) volume of water for small experiments.

C. Granulation sizing and milling

An optimized MADG formulation and process should not produce large lumps in the granulation that require sizing or milling. Therefore, once lubricant is blended in with the granulation, the result may be the final blend that can be directly used for tablet compression, encapsulation, or powder filling. At times, small amounts of lumps in the granulation may stem from material buildup on the blades, choppers, walls, or the bottom of the granulator during agglomeration. In such situations, it may be necessary to pass the granulation through a screen such as 10 mesh or any other suitable size. Often, sizing or sifting is needed only if the formulation or process contains imperfections.[11]

2. Materials and equipment

A. List of materials

Following listed materials were used in formulation and evaluation of tablet dosage form of Metoprolol succinate as model drug.

Table 1: List of materials

Sr. no.	Materials	Role	Source
1	Metoprolol Succinate	Active Pharmaceutical Ingredient	Wockhardt Limited, Aurangabad
2	Lactose monohydrate	Filler/Diluent	Atra Pharmaceuticals, Aurangabad
3	Maize starch	Disintegrant	Qualigens fine chemicals, Mumbai
4	PVP K 30	Binder	Atra Pharmaceuticals, Aurangabad
5	Prosolve SMCC 90	Moisture adsorbing agent	Lupin pharmaceutical, Aurangabad
6	Sprees-B 818	Moisture adsorbing agent	Grain processing USA
7	Magnesium stearate	Lubricant	Atra Pharmaceuticals, Aurangabad
8	Aerosil	Glidant	Atra Pharmaceuticals, Aurangabad

B. List of equipment used

Following listed equipments were used in formulation and evaluation of tablet dosage form of Metoprolol succinate as model drug.

Table 2: List of equipments

Sr. No.	Equipment	Manufacturer
1	Tablet compression machine (Single rotary)	Rimek mini press-II, Gujrat, India.(Karnavati)
2	Disintegration apparatus	ElectrolabTDT
3	Dissolution Test apparatus.	Electrolab TDT.
4	UV Spectrophotometer.	Shimadzu UV-1800,Japan
5	FTIR Spectrophotometer	Jasco FTIR -4100, Japan.
6	Differntial Scanning Colorimetry	Schimadzu DSC-60
7	Digital Weighing Balance.	Shimadzu AX200
8	Digital pH Meter.	Equiptronics EQ-610
9	Friability test apparatus EF-2 (USP)	Electrolab, Mumbai
10	Hardness tester	Coslab Pvt. Ltd, Mumbai
11	Tapp density apparatus	Remi Moters, Mumbai.
12	Thickness gauge (vernier calliper)	Coslab Pvt. Ltd, Mumbai.
13	Stability chamber	Remi, Mumbai

EXPERIMENTAL

A.PREFORMULATION STUDIES

Characterization of drug

- **Colour and appearance**
- **Melting point**

Melting point of MTS was determined by taking a small amount of sample in a capillary tube placed in Thiele's melting point apparatus.

- **Solubility**

Solubility study was carried out as per the I.P.2007.

➢ **UV spectra**

Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of phosphate buffer pH 6.8 and volume was made up to 100 ml to make a stock solution (100µg/ml). 1ml of aliquot was withdrawn from the stock solution . The resultant solution was scanned from 200 to 400 nm.

➢ **Fourier transform infra-red spectra**

The drug sample and potassium bromide powder was mixed. The baseline correction of FTIR (4100 Jasco) was carried out using dried KBr and then spectrum of dried mixture of drug and KBr was recorded by placing the powder in the light path and scanning the sample over the range of 4000-400 cm^{-1}

➢ **Differential scanning calorimetry (DSC)**

Accurately weighed samples of Metoprolol succinate (4.4 mg) were hermetically sealed in aluminium pan and heated at a constant rate of 20°C/min over temperature range of 70 to 300°C. The DSC thermogram was recorded and reported.

➢ **Calibration curve of Metoprolol succinate**

- **Preparation of stock solution**

The stock solution was prepared by dissolving 50mg in 50ml of Phosphate buffer pH-6.8 to obtain concentration of 1000 µg/ml. 10ml of aliquot was withdrawn from the stock solution and volume was made up to 100 ml using Phosphate buffer pH-6.8 to obtain the concentration of 100µg/ml.

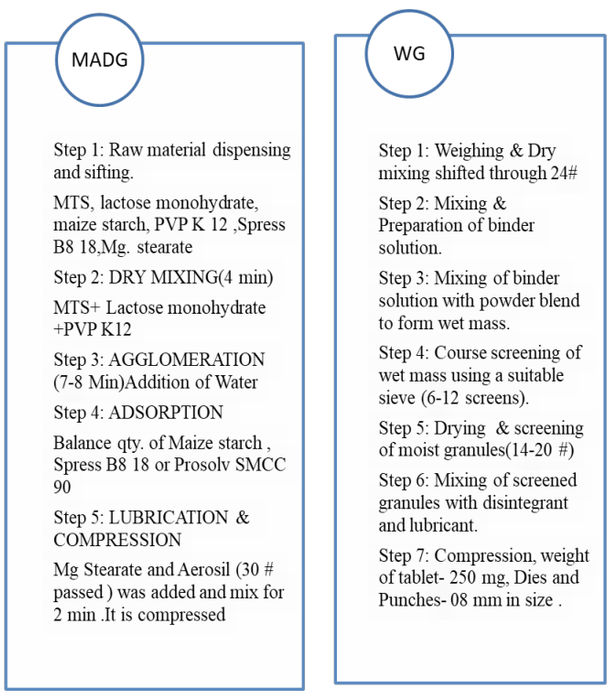
- **Preparation of serial dilutions**

Different aliquots were prepared from stock solution in series of concentrations from 2-10µg/ml. The λ_{max} was found to be 222 nm from UV spectrum of MTS. Absorbance was measured at 222 nm against Phosphate buffer pH 6.8 as blank on a UV Visible Spectrophotometer (UV-1700 SHIMADZU). The calibration curve was prepared by plotting absorbance versus concentration of Metoprolol succinate.

B.FORMULATION STUDY

➢ **Table 3: Preliminary trial batches**

Ingredients for tablet	Quantity in each Formulation (mg/tab)						
	A	B	C	D	E	F	WG
Metoprolol Succinate	50	50	50	50	50	50	50
Lactose monohydrate	169.38	166.38	164.38	169.38	166.38	164.38	169.38
Maize starch	12.5	12.5	12.5	12.5	12.5	12.5	12.5
PVP K-12	5	5	5	5	5	5	5
Water	0.2	0.25	0.5	0.2	0.25	0.5	-
Sprees B 818	5	8	10	-	-	-	-
Prosolv SMCC 90	-	-	-	5	8	10	-
2% starch paste	-	-	-	-	-	-	q. s.
Aerosil	3.12	3.12	3.12	3.12	3.12	3.12	3.12
Magnesium stearate	5	5	5	5	5	5	5
TOTAL	250	250	250	250	250	250	250



Preliminary trail batches were prepared using Spress B8 18 and Prosolv SMCC 90 for preliminary evaluation. Both batches shows a good physicochemical parameters but batches with Spress B8 18 were superior in terms of some evaluation parameters so for the optimization batches were prepared only with Spress B8 18. The wet granulation batch is also prepared using above formula to have comparison between final optimized MADG batch and WG batch. The formulation of tablet using MADG and WG is done according to above outline

➢ **Factorial Design**

Instead of repeating experiments for each independent variables or factor, we can design a more efficient experiment that evaluates the effect of two or more factors at the same time. These types of design are referred to as factorial design.

In the present study, a 3^2 full factorial design was employed containing 2 factors evaluated at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of Water (X1) and Sprees (X2) were selected as independent variables. The time required for dissolution of drug selected as dependent variable.

Table 4: Value codes of factorial design

Coded value	X_1(%)Water	X_2 (gm) Spress B8 18
-1	6	8
0	8	10
+1	10	12

X1 = WATER X2= SPRESS B8 18

Table 5: Translation of coded values for 3^2 factorial experimental designs

Formulation code	Variable level code	
	X_1	X_2
Formulation F1	-1	-1
Formulation F2	-1	0
Formulation F3	-1	+1
Formulation F4	0	-1
Formulation F5	0	0
Formulation F6	0	+1
Formulation F7	+1	-1
Formulation F8	+1	0
Formulation F9	+1	+1

Table 6: Formulation of 3^2Factorial Design Batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
MTS	50	50	50	50	50	50	50	50	50
Lactose	154.38	149.38	144.38	154.38	149.38	144.38	154.38	149.38	144.38
starch	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
PVP K- 12	5	5	5	5	5	5	5	5	5
Water	15	15	15	20	20	20	25	25	25
Sprees	20	25	30	20	25	30	20	25	30
Aerosil	3.12	3.12	3.12	3.12	3.12	3.12	3.12	3.12	3.12
Mg.stearate	5	5	5	5	5	5	5	5	5
Total	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

EVALUATION

Evaluation of flow properties of powder blends of factorial batches.

The quality of tablet depends upon the quality of powder from which it is prepared. Therefore, it is quite necessary to evaluate the powder and see whether it is of required quality or not. The powder of factorial batches were evaluated for Bulk density, Tapped density, Carr' index (compressibility), Angle of repose and Hausner ratio.

➢ **Angle of repose**

It is a maximum angle possible between the surface of pile and the horizontal plane. The lesser the angle of repose, more is the free flowing powder and vice-versa. The angle of repose for the powder of each formulation was determined by the funnel method. The fixed amount (5 g) of powder mass was allowed to flow out of the funnel orifice fixed at a height of 2.5 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of the powder from the funnel mouth forms a pile of powder at the surface; it was continued until the pile touches the stem tip of the funnel. The base of the pile was marked and the radius of the powder cone (r) and height of the pile (h) was measured. Angle of repose was then calculated with the use of the following formula

$\tan \theta = (h)/r$

Where,

h = height of piler

r = radius of the pile base

Table 7: Relationship between Angle of repose (θ) and flowability

Sr. no.	Angle of repose (θ)	Flowability
1	< 20	Excellent
2	20-30	Good
3	30-35	Passable
4	>40	Very poor

➢ **Bulk density**

Apparent bulk density (b) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density (b) was calculated using following formula:

Bulk Density = M / Vb

➢ **Tapped density**

The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tapping). The minimum volume (Vt) occupied in the cylinder and weight of the blend was measured. The tapped density (t) was calculated using following formula.

Tapped Density = M / Vt

➢ **Carr's index**

The Carr's index is expression that shows the compressibility of the powder. It is calculated by using the formula,

Carr's Index = [(Tapped Density – Bulk Density) / Tapped Density] x 100

The Carr's index is frequently used as flowability characteristic.

Table 8: Relationship between % Compressibility index and Flowability

Sr. no.	%Compressibility Index	flowability
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Very very poor

➢ **Hausner's ratio**

The Hausner's ratio (H) is an indication of flowability of the powder. It is calculated by the formula-

$$H = \frac{\rho_t}{\rho_b}$$

Table 9: Relationship between Hausner's Ratio and flowability

Sr. No.	Hausner's Ratio	Flow Property
1	0.0-1.25	Free flow
2	1.25-1.6	Cohesive Flow

Evaluation of Metoprolol succinate tablets

➢ **Appearance**

The thickness of tablet as a dimensional variable was evaluated. The tablet thickness was controlled within average value. The colour, odour and any other flaws like chips, cracks, surface texture, etc. are other important morphological characteristics were observed.

➢ **Hardness**

Tablet hardness is defined as force required to crushing the tablet in diametric compression test. The hardness was measured with Monsanto hardness tester. The tablets were placed diametrically between two plungers and the lower plunger is kept in contact of tablet to read as zero. The upper plunger is forced against a spring by turning the screw until tablet fractures.

➢ **Friability**

Twenty tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which revolves at 25 rpm for 4 minutes dropping the tablets through a distance of 6 inch with each revolution. This process was repeated for all formulations and the percentage friability was calculated.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets - Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Where; W1 = Initial weight of table. W2 = weight of tablet after rotation.

➢ **Weight variation test**

20 tablets were taken and average weight of the tablet was determined. The tablets were weighed individually and the weight variation was determined as per Indian pharmacopoeia.

Table 10: The tablets weight and their weight deviation allowed.

Average Weight of Tablet	% Deviation allowed
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 mg or more	5

➢ **Thickness and Diameter**

The thickness and diameter of tablets were determined with the help of vernier calliper. The average diameter and thickness of the tablet was calculated. The test passed if none of the individual diameter and thickness value deviated by ± 5% of the average.

➢ **Drug Content**

Randomly selected 5 tablets from each batch were crushed in a mortar and pestle. The crushed powder equivalent to 50 mg of Metoprolol succinate was taken and dissolved in 50 ml of distilled water (1000µg) then filtered through Whattman filter paper. The concentration of Metoprolol succinate was determined by measuring the absorbance at 222nm. Aliquots were taken from stock solution and diluted with distilled water and analyzed by UV-Visible Spectrophotometer.

➢ **In vitro dissolution profile of formulation batches**

In vitro drug release study was carried out using USP dissolution apparatus II paddle in pH 6.8 buffer for a period of 1 hrs.

➢ **Accelerated Stability Studies**

On the basis of In vitro evaluation of all the formulation batches for the various parameters, formulations were packed in thick aluminum foil and stored in ICH certified stability chambers for the accelerated stability studies. The tablets were stored in the stability chamber at the controlled conditions of temperature and relative humidity. The stability of the tablets was studied for the duration of 30 days at temperature $40^0C \pm 2^0C$ and 75% ± 5% relative humidity. The tablets were then evaluated for various parameters viz. thickness, hardness, and drug content and release studies.

3. Results and discussion

A.PREFORMULATION STUDIES

➢ **Drug identification**

The sample of Metoprolol succinate procured for study was identified. The sample was identified by melting point, UV spectrum, FTIR spectrum and differential scanning calorimetry.

➢ **Melting point**

The melting point of Metoprolol succinate was determined by capillary method and was found to be 135 ± 1.52 ºC, which is in good agreement with reported melting point.

Table 11: Melting Point of Metoprolol succinate

Sr. No.	Melting point (^{0}C)	Average (^{0}C)
1	136	136 ± 1.52^{0}C
2	138	
3	135	

➢ **Solubility**

Solubility of drug is determined in ellutropic series of solvent to explore polarity of compound.

Table 12: Solubility of Metoprolol succinate

Sr. No.	Solvents of ellutropic series	Solubility
1.	Water	Soluble
2.	Acetic acid	Soluble
3.	Methanol	Soluble
4.	Ethanol	Soluble
5.	Propanol	Insoluble
6.	Acetonitrile	Insoluble
7.	Ethyl acetate	Insoluble
8.	Acetone	Insoluble
9.	Dichloromethane	Insoluble
10.	Diethyl ether	Insoluble
11.	Chloroform	Insoluble
12.	Toluene	Insoluble
13.	n-Hexane	Insoluble

Metoprolol succinate had maximum solubility in water and other highly polar solvents.

➢ **UV spectra**

The UV spectrum of Metoprolol succinate solution (100µg/ml) exhibited wavelength of absorbance maximum at 222 nm which complies with the reported.

➢ **Fourier transforms infra-red spectra**

The FTIR spectrum of Metoprolol succinate was recorded over a range of 4000 cm^{-1} to 400 cm^{-1}.

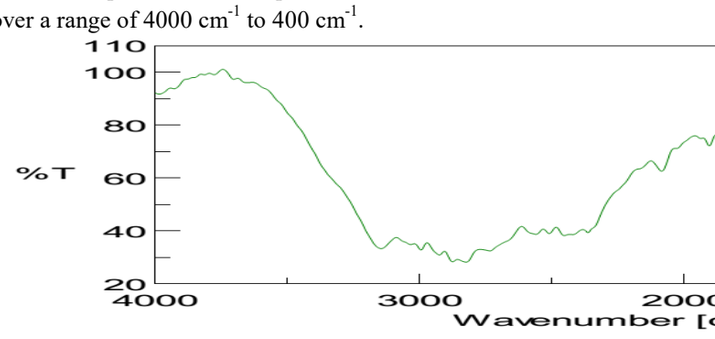


Fig. no.9.1: Infrared Spectrum of Metoprolol succinate

Table 13: Assignment for principal Infrared absorption bands of MTS.

Sr. No.	Functional group	Frequency(cm^{-1})
1	O-H	3313.15
2	C-O-C	1165.15
3	C_6H_5	1528
4	$-CH_3$	2928.73
5	-NH	2833.13

➢ **DSC Study of Drug**

DSC thermogram of Metoprolol succinate showed one endothermic peak of fusion, having peak maximum of 137.90°C. This was in accordance with the reported. (Fig.No.9.2)

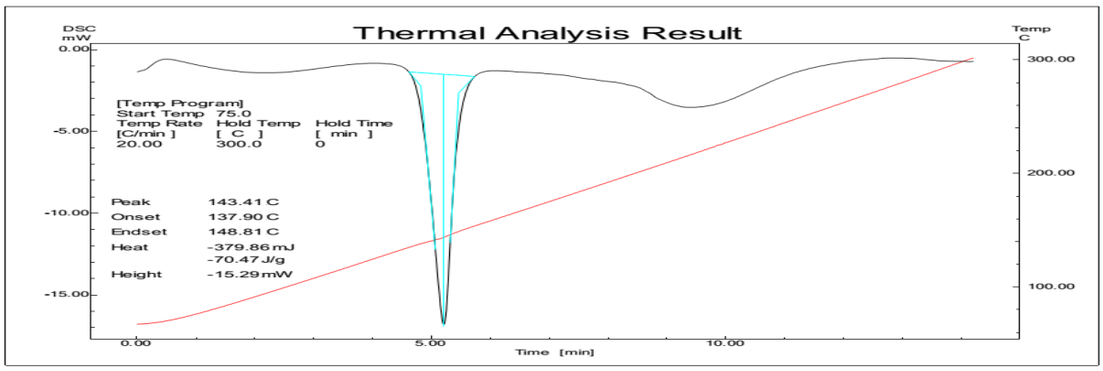
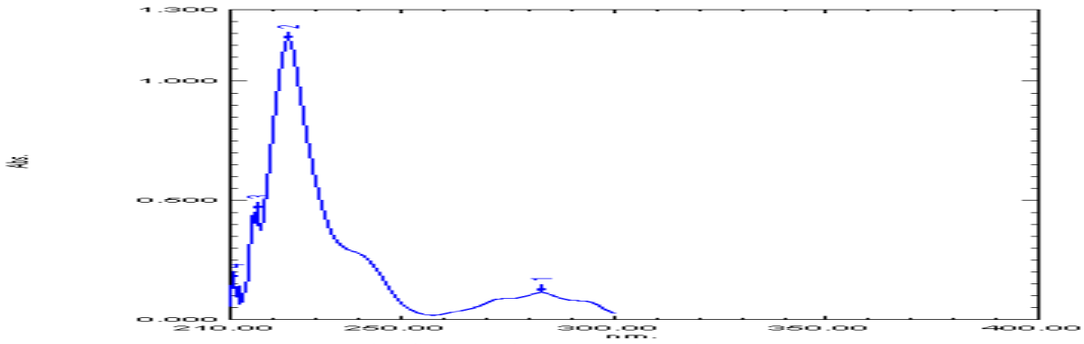


Fig. No.9.2: DSC Thermogram of Metoprolol Succinate

➢ **Calibration curve of Metoprolol succinate**

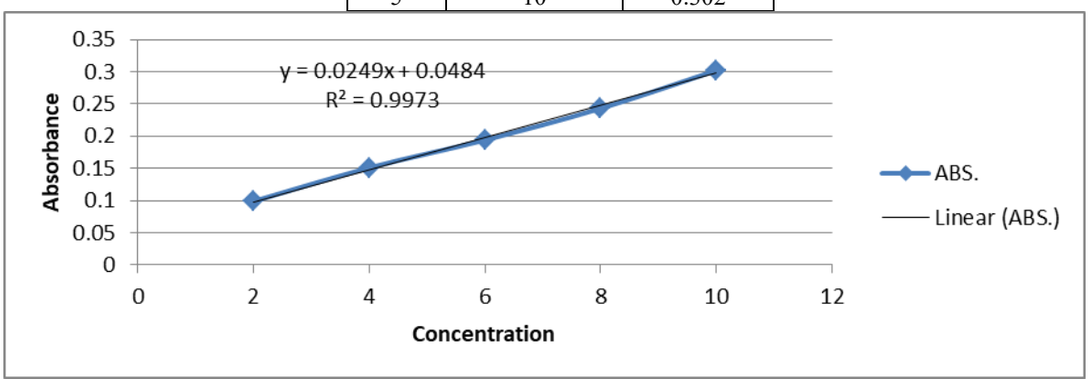
The standard solution of Metoprolol succinate showed linear curve with correlation coefficient of 0.997. The UV spectrophotometric method was selected for estimation of Metoprolol succinate. The UV spectrum exhibited maximum absorbance (λmax) at 222 nm. The standard calibration curve exhibited good coefficient of correlation (fig No.10.3)



UV Absorption Spectra of Metaprolol Succinate

Table 14: Calibration curve of Metoprolol Succinate in buffer pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance
1	2	0.099
2	4	0.151
3	6	0.194
4	8	0.243
5	10	0.302



Standard calibration of Metaprolol Succinate

Table 15: Standard calibration curve statistics

Sr. No.	Properties	Values
1	Absorbance Maximum	222
2	Slope	0.024
3	Intercept	0.048
4	Correlation Coefficient (r^2)	0.997

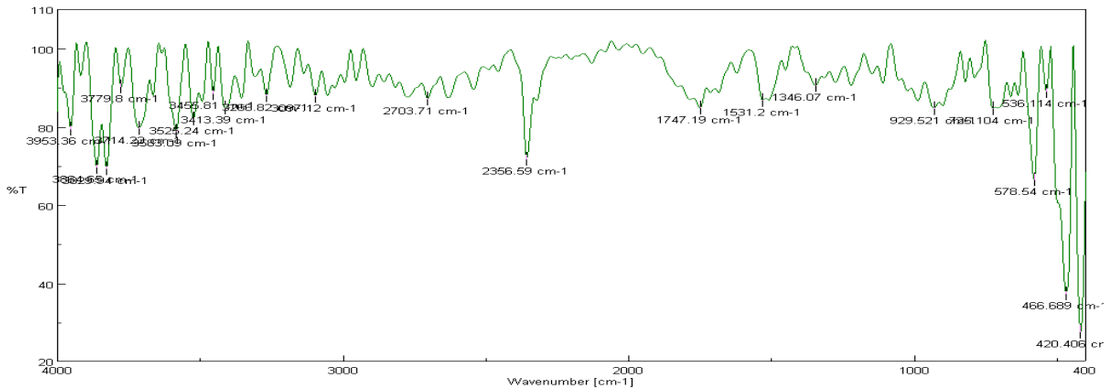
UV calibration of the MTS are done with 2-10 µg/ml show the absorbance in the (Table.no.9.4) shows the linear graph of the MTS. The standard calibration curve shown in (Fig.No.9.4)

➢ **Characterization of Excipients**

Table 16: Characterization of Sprees B8 18

Test	Specification	Results

Appearance	White	Complies
Solubility	Slightly Soluble in cold water	Complies
Density	1.5 g/cm^3	1.5 g/cm^3
Melting point	261-263^{0}C	261.2^{0}C



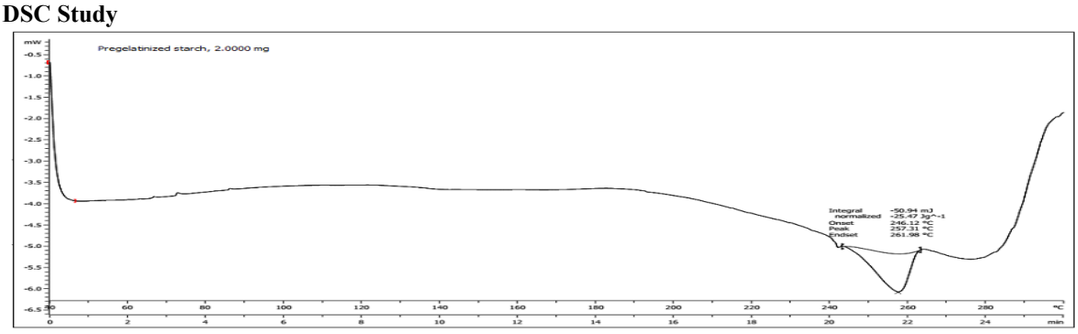
Infrared Spectra of Sprees B8 18

Table 17: Assignment of principal Infrared absorption bands of Spress B818

Functional group	Characteristic peak
N-H stretch	3443
N-H_2 stretch	3200
C-H stretch	2969
C-H stretch	2925
C=O	1685
Ortho –substituted aryl	1395
C=O symmetrical stretch	769

FTIR study of the drug polymer was done result are shown in (table No.10.7) the functional group present in polymer compared with the mentioned in the NF .The various group present as N-H stretches -primary amine , N-H2 streches – secondary amine, C-H stretches- alkyl group, C= O stretch anhydride, amine , aromatic ,alkenes, ortho substituted aryl . FTIR confirmed from above it is Spress B8 18 Pregelatnised starch NF.

- **DSC Study**



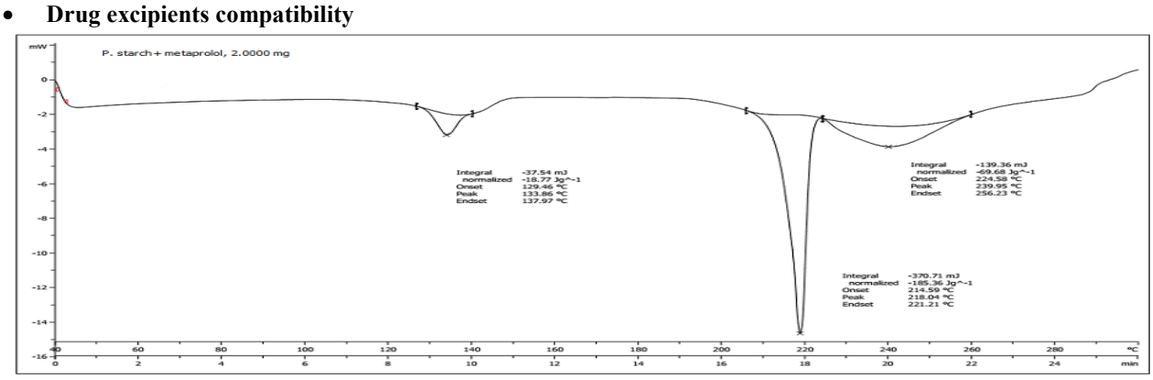
DSC Spectra of Sprees B8 18

DSC thermogram of Sprees B 8 18showed one endothermic peak of fusion, having peak maximum of 261.90°C show in the figure. This was in accordance with the reported. From the endothermic peak it is concluded a polymer SPRESS B8 18 is stable endothermically stable for the formulation.

- **INTERACTION BETWEEN DRUG AND POLYMER**

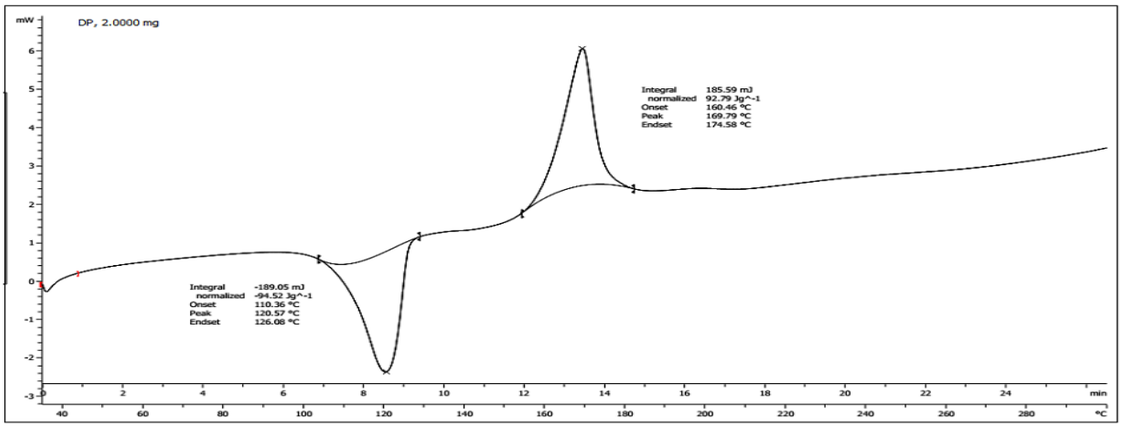
To check the interaction between drug and polymers, used in the formulation, DSC studies were performed. The Drug-polymer mixtures are given below spectra.

- **Drug excipients compatibility**



DSC Analysis of Drug + Sprees B8 18

The endothermic peak at 136.32ºC and 256.04^{o}C can be attributed as melting point of Metoprolol succinate and Spress B8 18 respectively show in (fig.no.10.7) Thus the thermogram showed that the Metoprolol succinate, Spress B8 18 pregelatinized starch are compatible with each other since there is no significant difference in endothermic peak of pure drug and physical mixture of drug with other excipients.



DSC Analysis of Drug + PVP K -12

The endothermic peak at 136.32ºC can be attributed as melting point of Metoprolol succinate and PVP K -12. Thus the thermogram showed that the Metoprolol succinate and PVP K-12 are compatible with each other since there is no significant difference in endothermic peak of pure drug and physical mixture of drug with other excipients. In the formulation they show the compatibility.

B. FORMULATION STUDIES

➢ **Precompression Characteristics of Powder Blend for Preliminary Batches**

From the powder characteristics i.e. angle of repose, compressibility index and Hausner's ratio etc., it was concluded that the powder possesses good, excellent and free flowing characteristics.

Table 18: Flow properties of preliminary trial batches powder.

Parameters	F1	F2	F3	F4	F5	F6
Bulk Density	0.282± 1.04	0.289 ± 1.02	0.296± 1.14	0.287± 1.52	0.313± 1.88	0.307± 1.93
Tapped Density	0.342 ± 1.07	0.358 ± 1.17	0.365 ± 1.47	0.345± 1.97	0.342± 1.67	0.345± 1.57
Carr's Index (%)± SD	18.01± 1.83	19.14 ± 2.83	19.09 ± 4.13	16.85± 5.35	20.94± 4.81	17.83± 2.73
Hausner Ratio (%)	1.245 ± 1.02	1.231 ± 1.04	1.235 ± 1.08	1.206± 1.048	1.267± 2.02	1.225± 2.01
Angle of Repose(^{0})	19.17± 1.12	18.17 ± 1.62	16.58 ± 1.92	24.59± 1.12	23.27± 1.99	26.17± 2.12
Loss on drying (%)	2.160	3.482	2.34	3.08	4.56	4.95
Amount of Fines (%)	10.24	12.32	12.99	14.24	15.07	14.97
Drying Time (Minutes)	2.0	2.5	2.8	3.1	3.8	4.2

(All the values are represented as mean ± s.d; n=3)

From the above results it can be concluded that amount of fines of spressB8 18 was within 10 to 12% while prosolv shows 14 to 15%. Again the drying time for spress batch was found less than that of prosolv batch. The parameters like loss on drying and angle of repose also proves the superiority of spress batches over prosolv formulation batches. So the factorial batches were prepared with spress B8 18 only.

➢ **Evaluation of Tablet Characteristics for Preliminary batches:**

➢ **Physical Appearance:**

The tablets were observed visually for their physical appearances: such as colour and texture, & found that all the formulation is of good appearance having white to yellowish white colour and smooth surface texture.

➢ **Parameters for Tablet Evaluation:**

Formulated batches of tablet were evaluated for hardness, weight variation, thickness and diameter, percent friability, content uniformity, The results of all these were in compliance with specification of I.P. are indicated in Table no. 9.9

- Hardness and Friability:

The formulation showed hardness value in the range of to 4.16 to 5.08 Kg/cm^2. Another measure of tablets strength is friability. In present study, the friability value for all tablet formulation were found to be less than 1% indicate that the friability within the prescribed limit.

- Thickness and Diameter:

Thickness of all tablets formulation was found to be 2.33mm and diameter of the tablets was found to be about 8.01 to 8.03 mm.

- Drug Content Uniformity:

The drug content values were obtained between 98.5 and 102.62 % for all formulations, which was found satisfactorily within I.P., limits (not less than 90% and not more than 110%).

Table 19: Evaluation of Tablet Characteristics for Preliminary batches.

Parameters	F1	F2	F3	F4	F5	F6
Hardness(Kg/cm^2)±SD	3.92± 0.14	4.08 ± 0.15	4.65 ± 0.11	4.20 ± 0.16	5.16 ± 0.06	4.72 ± 0.27
Diameter (mm) ± SD	8.01 ± 0.06	8.02 ± 0.03	8.01 ± 0.06	8.03 ± 0.07	8.02 ± 0.01	8.01 ± 0.02
Thickness (mm)± SD	2.32 ± 0.01	2.30 ± 0.02	2.34 ± 0.01	2.31 ± 0.03	2.30 ± 0.01	2.33 ± 0.02
Friability (%)± SD	0.57 ± 0.10	0.51 ± 0.21	0.68 ± 0.11	0.72 ± 0.06	0.79 ± 0.09	0.53 ± 0.1
Disintegration time	8.1	8.3	8.6	12.3	12.9	13.1

- Weight Uniformity:

Table 20: Weight Variation test for preliminary trial batches of tablet formulation.

Sr. No.	Formulation A	Formulation B

1	Weight in mgs	Difference in weight	Percent Deviation	Weight in mgs	Difference in weight	Percent Deviation
2	251	1.3	0.81	254	4.4	2.7
3	252	2.3	1.4	252	2.4	1.49
4	249	0.7	0.43	248	2.4	1.49
5	254	4.3	2.69	250	0.4	0.24
6	247	2.7	1.69	248	2.4	1.49
7	248	1.7	1.06	248	2.4	1.49
8	250	0.3	0.187	249	1.4	0.87
9	248	1.7	1.06	250	0.4	0.24
10	250	0.3	0.187	252	2.4	1.49
	248	1.7	1.06	253	3.4	2.11
	Average of 10 tablets 249.7 mg			Average of 10 tablets 250.4 mg		
Sr. No.	Formulation C			Formulation D		
	Weight in mgs	Difference in weight	Percent Deviation	Weight in mgs	Difference in weight	Percent Deviation
1	253	2.2	1.36	252	1.1	0.68
2	252	1.2	0.74	255	4.1	2.54
3	252	1.2	0.74	248	2.9	1.80
4	250	0.8	0.49	250	0.9	0.55
5	250	0.8	0.49	252	1.1	0.68
6	253	2.2	1.36	253	2.1	1.30
7	252	1.2	0.74	253	2.1	1.30
8	249	1.8	1.11	247	3.9	2.42
9	247	3.8	2.36	249	1.9	1.18
10	250	0.8	0.49	250	0.9	0.55
	Average of 10 tablets 250.8 mg			Average of 10 tablets 250.9 mg		
Sr. No.	Formulation E			Formulation F		
	Weight in mgs	Difference in weight	Percent Deviation	Weight in mgs	Difference in weight	Percent Deviation
1	250	0.7	0.43	252	0.8	0.49
2	252	1.3	0.80	253	1.8	1.11
3	254	3.3	2.05	251	0.2	0.12
4	252	1.3	0.80	252	0.8	0.49
5	252	1.3	0.80	252	0.8	0.49
6	251	0.3	0.18	253	1.8	1.11
7	249	1.7	1.05	248	3.2	1.98
8	248	1.68	1.68	249	2.2	1.36
9	247	2.30	2.30	250	1.2	0.74
10	252	1.3	0.80	252	0.8	0.49
	Average of 10 tablets 250.7 mg			Average of 10 tablets 251.2 mg		

(All the values are represented as mean ± s.d; n=3)

The pharmacopoeial limits of deviation for tablets of more than130mg and less than 324mg are ± 7.5 % The average percentage deviation for all tablet formulation was found to be within the specified limits and hence all formulation complied with the test for uniformity of weight.

- **Evaluation of cumulative drug release.**

Drug release that is cumulative percentage of drug dissolution in phosphate buffer pH 6.8 for the period of 60 minutes at temperature 37^0C.Volume of dissolution media is 900 ml. Samples 10 ml each were withdrawn after 5,10,15,20.. And 60 minutes. To maintain the volume in dissolution vessel, 10 ml of fresh solution was replaced in each case after withdrawal of the sample and analyzed by using U.V. Spectrophotometer at 222nm wavelength and value are reported in table 21

- **Dissolution medium:** pH 6.8
- **Apparatus:** USP type II paddle
- **Speed:** 50 rpm
- **Volume of dissolution medium:** 900 ml

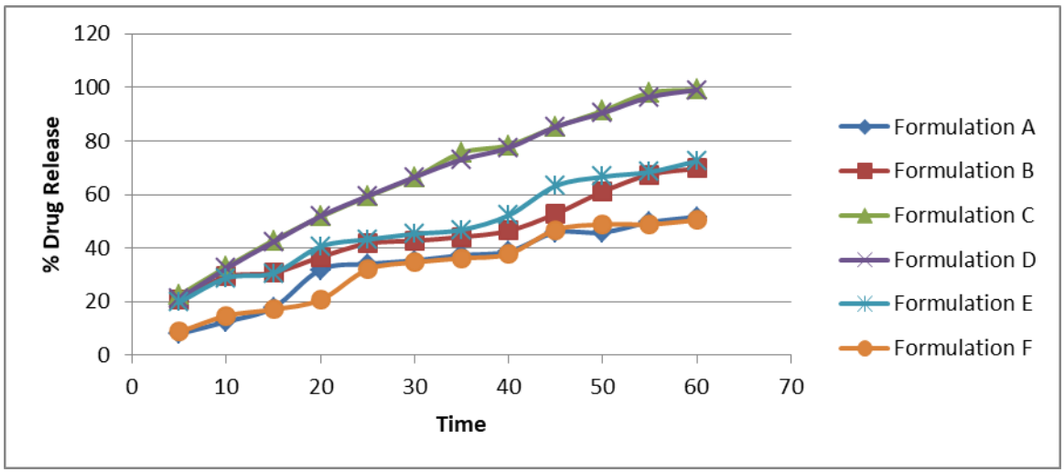
Table 21: Cumulative drug release for preliminary trial batches of tablet formulation.

Sr. No.	Formulation A			Formulation B		
	Time in minutes	Average %release	Standard Deviation	Time in minutes	Average %release	Standard Deviation
1	5	8.102	1.25	5	20.854	0.53
2	10	12.604	1.35	10	29.364	0.98
3	15	17.847	1.53	15	30.801	1.23
4	20	31.971	2.25	20	36.683	2.25
5	25	34.121	1.40	25	41.712	1.27
6	30	35.384	1.25	30	42.774	0.78
7	35	37.372	3.42	35	44.174	1.44
8	40	38.731	1.02	40	46.474	2.39
9	45	45.862	0.86	45	52.825	2.98
10	50	45.866	2.24	50	61.043	2.12
11	55	49.662	1.22	55	67.443	1.43
12	60	51.662	1.07	60	69.664	1.56
Sr. No.	Formulation C			Formulation D		

	Time in minutes	Average %release	Standard Deviation	Time in minutes	Average %release	Standard Deviation
1						
2	5	22.501	0.89	5	21.24	0.40
3	10	33.021	0.57	10	32.44	1.23
4	15	42.904	1.20	15	42.32	0.58
5	20	51.704	1.48	20	51.94	2.50
6	25	59.262	0.69	25	59.42	1.87
7	30	66.384	2.05	30	66.51	1.33
8	35	75.603	3.80	35	73.05	2.87
9	40	78.382	1.44	40	77.42	3.01
10	45	85.250	1.87	45	85.26	1.67
11	50	91.160	0.98	50	90.42	0.58
12	55	97.953	0.76	55	96.36	1.23
	60	99.056	1.77	60	99.01	1.85

Sr. No.	Formulation E			Formulation F		
	Time in minutes	Average %release	Standard Deviation	Time in minutes	Average %release	Standard Deviation
1	5	19.82	0.96	5	8.77	0.68
2	10	28.86	1.35	10	14.76	1.25
3	15	30.66	1.68	15	17.12	1.48
4	20	40.62	0.24	20	20.74	2.04
5	25	43.25	2.68	25	32.04	2.15
6	30	45.34	0.87	30	34.74	1.78
7	35	46.82	0.98	35	36.22	0.98
8	40	52.24	1.75	40	37.85	0.65
9	45	63.22	1.36	45	46.82	1.48
10	50	66.61	1.25	50	48.86	0.94
11	55	68.42	0.49	55	48.88	1.36
12	60	72.46	1.47	60	50.46	1.11

(All the values are represented as mean ± s.d; n=3)



Dissolution of Trial Batches

➢ **Evaluation of flow properties of powder blends of factorial batches**

Table 22: Evaluation of Powder blend of factorial batch

Formu-lation	Bulk Density (g/ cm^3)	Tapped Density	Carr's Index	Hausner Ratio	Angle of Repose	LOD (%)
F1	0.2012±0.94	0.2425±1.07	16.67±1.83	1.20±1.02	19.17±0.98	1.49
F2	0.2014±1.2	0.2157±2.06	15.54±1.83	1.05±1.04	16.17±0.87	1.85
F3	0.8402±1.69	0.25± 0.85	33.66±3.13	1.25±0.94	35.12±0.83	2.03
F4	0.250±1.85	0.345±1.011	16.85±3.35	1.64±1.24	18.59±0.84	1.25
F5	0.261±0.97	0.286±1.536	10.28±4.81	1.66±1.84	19.27±0.94	1.59
F6	0.912±1.03	0.298± 2.05	33.33±2.73	1.35±1.04	41.21±0.85	2.4
F7	0.811±2.07	0.240±0.513	35.69±1.51	1.32±0.84	41.56±0.93	3.58
F8	0.601±1.23	0.342±1.014	34.83±2.78	1.25±1.04	42.56±0.85	3.21
F9	0.2404±0.87	0.267±1.028	38.66±4.25	1.41±1.34	40.56±0.77	3.15
WG	0.5821±2.87	0.326±1.87	18.36±2.87	1.36±1.97	18.62±1.17	3.02

(All the values are represented as mean ± s.d; n=3)

➢ **Angle of repose**

The angle of repose can be correlated with type of flow of powder. The angle of repose 20 to 30º indicates the good flow while the angle of repose more 30º indicates poor flow properties and angle of repose below 20^0 indicates excellent flow properties. The angle of repose was found to be within the range of 16^0 to 20^0 indicating excellent flowability. Optimized all the batches F1, F2, F4,F5 shows the good flow.

➢ **Bulk density**

The bulk density of powder is important parameter in the compressibility of the powder. The bulk density was between 0.20 to 0.25 gm / all.

➢ **Tapped density**

The tapped density of powder is important parameters in the compressibility of the powder. The tapped density was found to be 0.32 to 0.40 gm/cm^2.

➢ **Carr's index**

The Carr's index is indicator of compressibility. The value below 21 % shows good compressibility. It was found to be 13 to 20 % indicating good compressibility

➢ **Hausner's ratio**

The value of ratio below 1.25 indicates good flow while above 1.25 indicates the poor flow. It was found to be batch .F1, F2, F4, F5 show 1.20 to 1.27 indicating good flowability.

➢ **Amount of fines**

The percentage of amount of fines of powder blend of factorial batch was found to be 13.65 while the percentage of fines of powder blend of WG formulation was found to be 14.10.

➢ **Drying Time**

The time required for drying of granules made by MADG was only 1 to 2 min. while a granule of WG requires 8 to 10 min.

Table 23: Evaluation of Tablets

Formulation	Wt. variation (mg)	Hardness (Kg/cm2)	%Friability	Thickness (mm)	DT (min)
F1	250 ± 1.08	4.08± 1.257	0.551	8.05±0.904	8.1
F2	250 ± 1.09	4.18± 1.211	0.496	7.97 ± 0.82	8.3
F3	250 ±1.58	3.67± 2.088	0.858	8.65±0.817	8.1
F4	250 ±2.54	4.28± 2.264	0.421	8.09±1.015	8.2
F5	250 ±2.96	4.18± 1.319	0.883	8.05±1.026	8.0
F6	250 ±1.56	4.18± 2.273	0.693	8.67±0.942	8.5
F7	250 ±1.48	4.79± 1.337	0.271	7.97±0.948	8.2
F8	250 ±2.98	4.89± 2.544	0.306	8.08±1.042	8.8
F9	250 ± 2.54	4.89± 2.544	0.556	8.14±1.025	8.3
WG	250 ±1.54	5.52± 1.440	0.611	8.17±1.725	25

(All the values are represented as mean ± s.d; n=3)

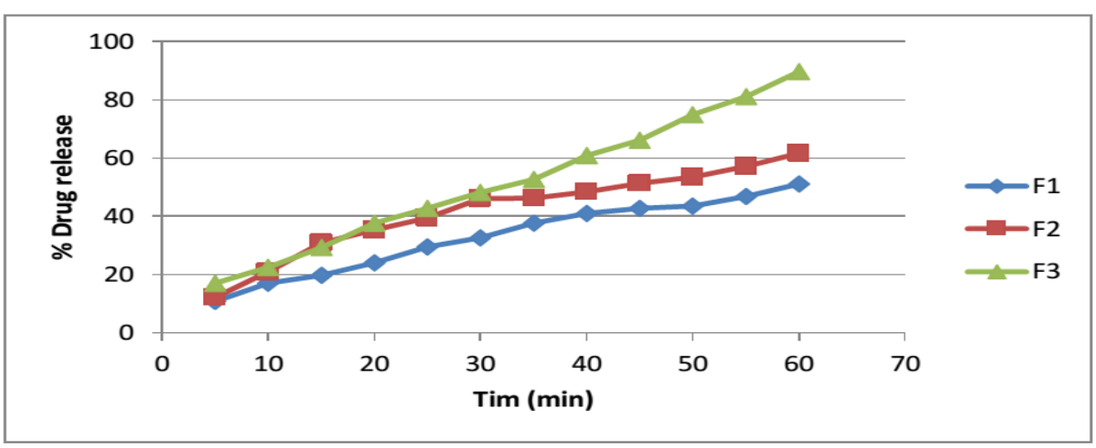
➢ **In vitro dissolution profile of formulation batches**

- **Dissolution medium:** pH 6.8
- **Apparatus:** USP type II paddle
- **Speed:** 50 rpm
- **Volume of dissolution medium:** 900 ml

Table 24: Cumulative Percent Drug Release (F1, F2, F3)

Time (Min)	F1	F2	F3
5	10.824 ±1.69	12.274 ±2.20	17.125 ±1.96
10	17.110 ±1.03	21.013 ±1.60	22.534 ±1.58
15	19.832 ±1.17	23.736 ±1.95	29.423 ±2.78
20	24.051 ±1.17	30.968 ±2.43	37.694 ±1.50
25	29.472 ±2.44	35.482 ±1.65	42.712 ±2.43
30	32.662 ±2.29	39.428 ±2.88	48.223 ±2.99
35	37.771 ±2.06	46.087 ±2.68	52.714 ±1.83
40	40.982 ±1.06	48.372 ±1.33	60.874 ±2.79
45	42.831 ±1.97	51.428 ±2.63	66.046 ±1.62
50	43.626 ±2.51	53.439 ±2.79	74.960 ±2.58
55	46.874 ±1.24	57.095 ±2.53	81.208 ±1.72
60	51.072 ±2.33	61.652 ±0.84	89.685 ±0.57

(All the values are represented as mean ± s.d; n=3)



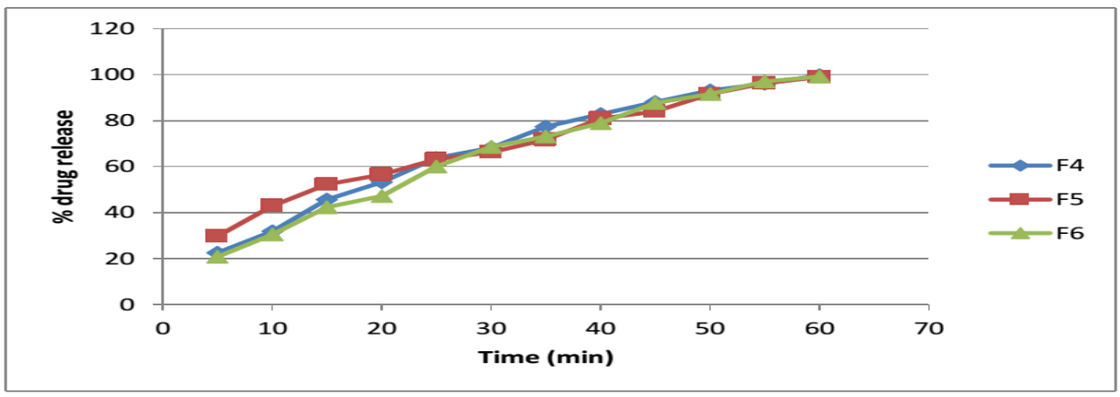
Dissolution of Factorial Batches (F1, F2, F3)

Table 25: Cumulative Percent Drug Release (F4, F5, F6)

Time (Min)	F4	F5	F6
5	22.543 ±1.30	29.721 ±0.95	20.880 ±1.66
10	31.884 ± 2.63	42.935 ±1.10	30.601 ±1.80

15	45.662 ±2.23	52.286 ±1.95	42.301 ±1.59
20	53.212 ±1.96	56.532 ±1.71	47.264 ±1.86
25	63.771 ± 2.72	63.261 ±2.46	60.153 ±2.83
30	68.171 ±1.88	66.264 ±1.96	68.625 ±1.25
35	77.413 ±2.48	71.742 ±1.63	73.196 ±1.39
40	82.902 ±1.68	80.812 ±2.54	78.982 ±2.12
45	88.093 ±1.54	83.904 ±1.62	87.601 ±1.67
50	93.201 ±2.89	91.496 ±3.32	91.521 ±2.61
55	96.082 ±2.53	96.241 ±1.70	96.961 ±3.37
60	99.734 ±0.96	98.901 ±1.06	99.162 ±0.97

(All the values are represented as mean ± s.d; n=3)

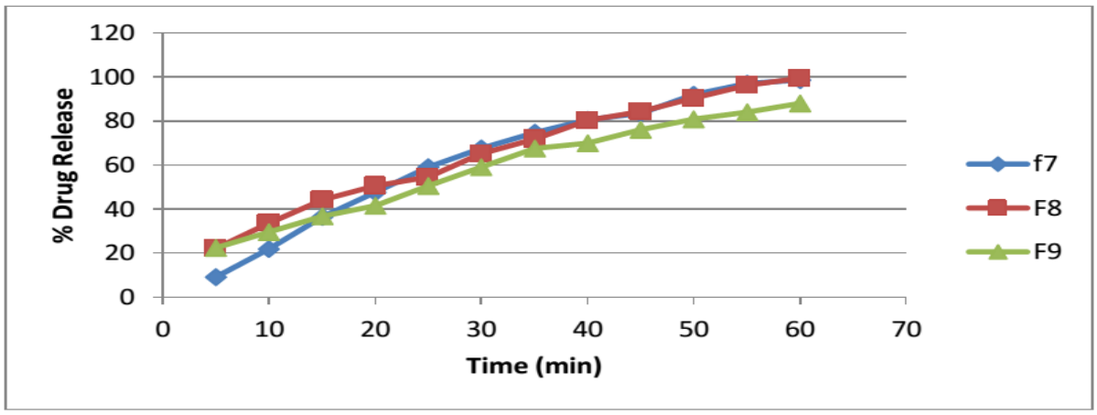


Dissolution of Factorial Batches (F4, F5, F6)

Table 26: Cumulative Percent Drug Release (F7, F8, F9)

Time (Min)	F7	F8	F9
5	9.3112 ±0.88	22.172 ±1.39	22.554 ±0.96
10	22.062 ±1.53	33.751 ±1.60	29.546 ±1.52
15	36.633 ±1.96	44.167 ±1.77	36.942 ±2.85
20	47.620 ±2.80	50.166 ±2.36	41.671 ±2.75
25	59.221 ±1.88	54.741 ±1.94	50.720 ±1.83
30	67.694 ± 2.29	65.312 ±0.91	59.241 ±0.93
35	74.810 ±1.92	71.971 ±1.99	67.761 ±1.52
40	80.756 ±1.32	80.472 ±1.81	69.923 ±2.73
45	83.545 ±2.30	84.450 ±1.76	76.051 ±1.92
50	92.032 ±1.59	90.464 ±2.42	80.891 ±1.53
55	97.237 ±1.47	96.345 ±1.39	84.222 ±2.72
60	98.844 ±0.90	99.581 ±1.43	88.244 ±1.72

(All the values are represented as mean ± s.d; n=3)



Dissolution of Factorial Batches (F7, F8, F9)

➢ **Statistical analysis by Design Expert Software**

Experimental design can be defined as the strategy for setting up experiments in such a manner that the information required is obtained as efficiently and precisely as possible. The factorial experimental designs are suitable over traditional optimization in terms of minimum number of experiments and ease in evaluation of statistical significance of independent factors on dependent variables. The factorial design requires lesser efforts than that of traditional optimization methods. The factorial design can serve as an essential tool to understand the complexity of mechanisms of pharmaceutical formulations. The polynomial equations are used to evaluate the statistical significance of the obtained responses. The quadratic model obtained from the regression analysis used to build a 3-D graphs in which the responses were represented by Sloped surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots.

Graphical presentation of the data helped to show the relationship between the response and the independent variables. The information given by graph was similar to that of mathematical equations obtained from statistical analysis.

➢ **Equation:**

Final Equation in Terms of Coded Factors:

drug release = +98.55+14.04 * A+4.57 * B-12.30 * A * B-17.75 * A^2+1.08 * B^2

Final Equation in Terms of Actual Factors:

drug release = - 483.68111+108.79125 * water+21.50833 * spres-3.07563 * water * spres-4.43833 *water^2+0.26917*spres^2

The 3^2 full factorial designs were selected to study the effect of independent variables Water (X1), Sprees B8 18(X2) on dependent variables i.e. Drug Release at 5 th min.(Q1) and Drug Release at 60 th min.(Q12).

➢ **ANOVA study**

Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings. Table no. shows ANOVA for the dependent variables. The coefficients of X1 and X2 were found to be significant at p <0.05, hence confirmed the significant effect of all the variables on the selected responses.

Increasing the concentration of the polymer resulted in the decrease in the release of Metoprolol succinate. Overall all the variables caused significant change in the responses. ANOVA and Multiple regression analysis were done using Design Expert 7.0.7.1 software.

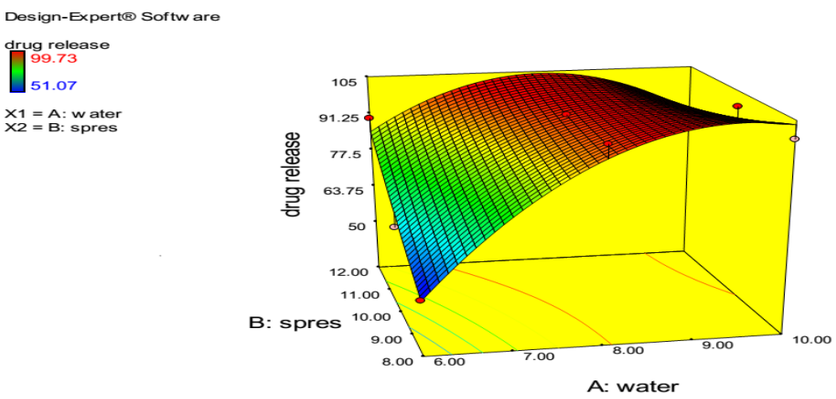
The model F value calculated was implied the models were significant. There were 2.75 % and 1.06 % chance that a "Model F-value" which could occur due to noise. Similarly R- squared was near to zero which led to good model. The values of Probe >F were less than 0.05, which indicated model terms were significant.

The Adeq-Precision was the measure of the signal to noise ratio. A ratio > 4 was desirable. In our case the Adeq-Precision values were indicated an adequate signal

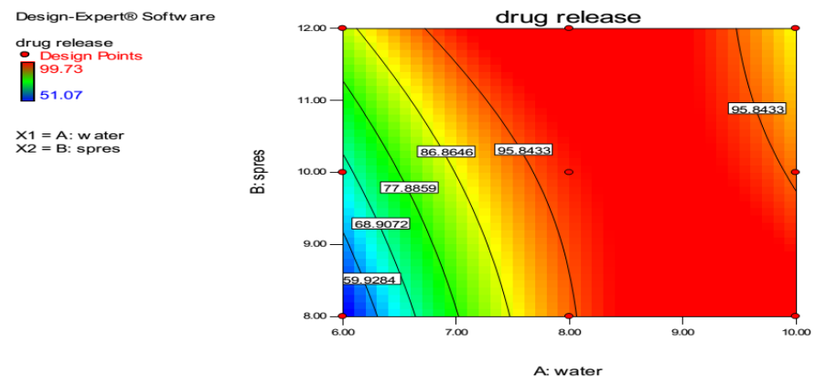
Table27: % Drug release: ANOVA for response surface quadratic model

Source	Sum of squares	df	Mean square	F-value	Pvalue prob>F	Model(Significant/Non -Significant)
Model	2546.87	5	509.37	10.63	0.0399	Significant (Linear)
A-water	1183.29	1	1183.29	24.69	0.0157	
B-spress	125.49	1	125.49	2.62	0.2040	
AB	605.41	1	605.41	12.63	0.0380	
A^2	630.36	1	630.36	13.15	0.0361	
B^2	2.32	1	2.32	0.048	0.8400	
Residual	143.76	3	47.90			
Cor total	2690.63	8				

➢ **Response Surface Plot**

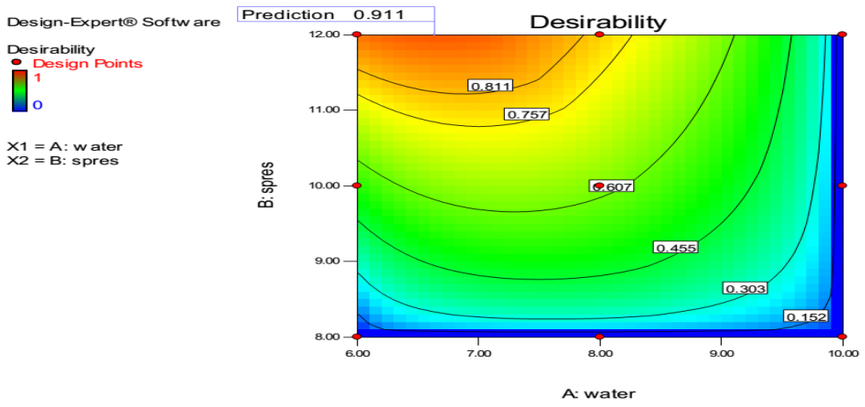


Surface response plot



Contour plot

The formulation F4 was selected as the model formulation. Drug Release was evaluated and found within the limits.



Desirability

Table 28: Optimization (Model Validation)

Sr. no.	Water	Spress	Drug release	Desirability	Selected/Not selected
1	8	8	98.92	1	Selected

➢ **Accelerated Stability Studies**

The stability of the tablet formulation (F4) was studied for the duration of 30 days at temperature $40^0C \pm 2^0C$ and 75% ± 5% relative humidity. The tablets were then evaluated for various parameters viz. Thickness, hardness, and drug content and release studies. Following results were observed in the Table.No.9.21

Table 29: Drug content before stability study

Absorbance (nm)	% Drug content
0.925	95.98

Table 30: Evaluation of Tablets (Stability).

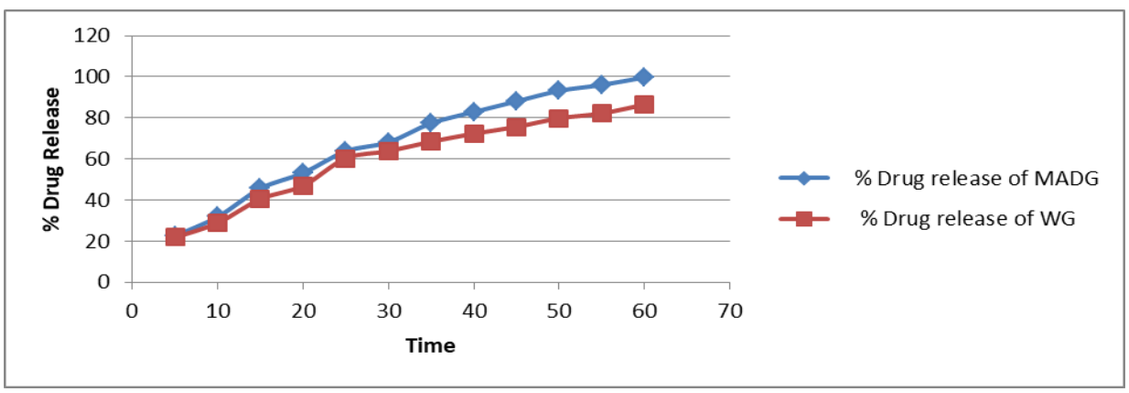
Batch Code	Thickness	Hardness	Wt. uniformity	% drug content
F4	8.62 ± 0.071	4.12 ±0.45	248 ± 0.48	95.96±0.19

Table 31: Comparison between optimized formulation and wet granulation formulation.

Properties	Optimized formulation(F4)	WG formulation
Amount of fines(%)	13.65	14.10
Angle of repose	18.59	18.62
Loss on Drying	1.25	3.02
Drying Time	2-3 Minutes	10-12 Minutes
Hardness	3-4 Kg/ cm^2	5-6 Kg/ cm^2

Table 32: Cumulative release of drug from two batches of tablets prepared by MADG (F4) and Conventional Wet granulation.

Time (min.)	% Drug release of MADG	% Drug release of WG
5	**22.543**	**21.803**
10	**31.884**	**28.924**
15	**45.662**	**40.502**
20	**53.212**	**46.982**
25	**63.771**	**60.341**
30	**68.171**	**63.840**
35	**77.413**	**68.452**
40	**82.902**	**72.758**
45	**88.093**	**75.211**
50	**93.201**	**79.817**
55	**96.082**	**82.221**
60	**99.734**	**86.481**



Dissolution of MADG batch and WG batch.

4. Conclusion

The old phrase “Time is Money” has never been more accurate than in today’s world. With the current economy, companies are looking at every opportunity to cut costs, including manufacturing costs. There is great value in production processes that can be shortened, but still produce a high-quality, effective end product. In the manufacturing of tablets, direct compression is always the first option investigated. However, if direct compression does not produce a quality tablet, the formulator must use granulation. Granulation processes take time and add additional cost to the formula. A new trend in granulation, which saves both time and money, is Moisture Activated Dry Granulation. Since minimal moisture is needed in this specialty granulation process, no drying time is required, shortening the processing time greatly. The granulation can be “dried” using a new specialty starch from GPC, like Spress B8 18 and prosolv SMCC 90.

Again changing regulatory compliances are requiring enhancement of product quality which is coming up in terms of increasing product output, decreasing product through put time, reducing labour and energy cost, this urge for development had brought revolution in granulation technology. So various innovative approaches have been explored to simplify and control the granulation process and improved quality of produced granules. Numerous active substances are sensitive to the heat and presence of relatively high amount of moisture. Moisture may stem from the excipients used in the formulation or from the manufacturing process, e.g. aqueous granulation, this can pose significant problems in the manufacture of pharmaceutical formulations and dosage forms containing such active substances. So the presence of moisture or requirement of heat as processing parameter is particularly undesirable if the active substance is prone to chemical degradation and/or physical phase transitions into an undesired crystalline and/or amorphous form (polymorphism) when being in contact with water or water-containing solutions. So MADG is developed to overcome these problems by eliminating one step of drying.

It is also developed in response to the difficulties experienced with wet granulation, in terms of endpoint, drying and milling. Wet granulation process endpoint is very sensitive to granulation time and shear. The wet granules need to be dried to a narrow range of moisture contents, which is difficult..

In the present work, MADG is compared with WG and found equally efficient or we can say that more efficient than conventional wet granulation technique. It can effectively utilize for high dose and high volume drug also.

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