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A QbD Approach on Pharmaceutical Development of Diazepam Oral Disintegrating Tablet

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ABSTRACT:

This study reports the QbD on Pharmaceutical Development of Diazepam Oral Disintegrating Tablet. The concept of quality by design (QbD) has recently gained importance by application of design of experiments approach (DoE). QbD describes a pharmaceutical development approach especially in formulation design & development and manufacturing processes for the purpose of maintaining and improving the product quality. There are various elements of QbD are there such as Quality Target Product Profile (QTPP) ,Critical Quality Attributes (CQAS), Quality Risk (Assessment) Management (QRM), Design Space etc. The present work is aimed in the application of quality by design (QbD) concept especially Target Product profile in the formulation development of Diazepam tablet.

Keywords: Quality by design, Diazepam, Oral Disintegrating Tablet

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INTRODUCTION

Orally Disintegration Tablets

Historical Development

Despite the remarkable development in drug delivery technology, orally drug delivery remains the preferred route for administration of drugs due the accurate dosage, low-cost of therapy, ease of administration and patient compliance.(1) In this case, tablets and capsules represents the most popular forms among oral drug delivery systems, occupying a large portion of oral dosage forms that are presently available. However, traditional tablets and capsules may have some inconvenient for patients with swallowing difficulties, especially paediatric and geriatric patients, people with conditions related to impaired swallowing, and for treatment of patients when compliance may be difficult (e.g., for psychiatric disorders). Moreover, orally administered conventional tablets or capsules can be a problem for travelling patient with limited access to water. To overcome these difficulties, a large number of solid oral dosage forms have been developed, as the orally disintegration tablets (ODTs).

Orally disintegrating tablets, classification assumed by United States Food and Drug Administration (FDA), is the general form of nomenclature for tablets that disintegrate rapidly or instantly in the oral cavity. In its turn, European Pharmacopoeia (Ph. Eur.) adopted the term orodispersible tablets. Despite the similarity between the names, they have owns its definition. The earliest United States regulatory definition for an ODT consisted in "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue". (2) More recently, FDA approved a new guideline which recommend an *in vitro* disintegration time less than 30 seconds, when examined by the disintegration test or an alternative method, on United States Pharmacopeia (USP). (3) Also, it suggests a tablet weight not more than 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an ODT for both

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patients and regulators. [4] According to Ph. Eur., "orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed". It also, should disintegrate within 3 minutes, when based on Ph. Eur. disintegration test method for tablets or capsules. [5]

MATERIALS AND METHOD

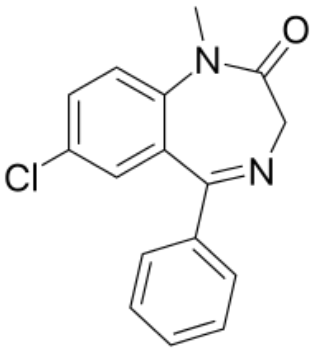
DRUG PROFILE

Drug Profile of Diazepam

Proper Name: Diazepam

Chemical Name: 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-one

Structural Formula:



Description: Diazepam is used in the treatment of anxiety, insomnia, panic attacks and symptoms of acute alcohol withdrawal. It is also used as a premedication for inducing sedation, anxiolysis, or amnesia before certain medical procedures (e.g., endoscopy). In 2020, it was approved for use in the United States as a nasal spray to interrupt seizure activity in people with epilepsy. Diazepam is the most commonly used benzodiazepine for "tapering" benzodiazepine

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dependence due to the drug's comparatively long half-life, allowing for more efficient dose reduction. Benzodiazepines have a relatively low toxicity in overdose.

Molecular Weight: 284.74 $g \cdot mol^{-1}$

Physical Form: solid white or yellow crystals.

Solubility: As per BP, it as being very slightly soluble in water, soluble in alcohol, and freely soluble in chloroform.

Melting Point: 131.5 to 134.5 °C.

Mechanism of action

Benzodiazepines are positive allosteric modulators of the GABA type A receptors (GABAA). The GABAA receptors are ligand-gated chloride-selective ion channels that are activated by GABA, the major inhibitory neurotransmitter in the brain. Binding of benzodiazepines to this receptor complex promotes the binding of GABA, which in turn increases the total conduction of chloride ions across the neuronal cell membrane. This increased chloride ion influx hyperpolarizes the neuron's membrane potential. As a result, the difference between resting potential and threshold potential is increased and firing is less likely. As a result, the arousal of the cortical and limbic systems in the central nervous system is reduced.

The GABAA receptor is a heteromer composed of five subunits, the most common ones being two αs, two βs, and one γ (α2β2γ). For each subunit, many subtypes exist (α1–6, β1–3, and γ1–3). GABAA receptors containing the α1 subunit mediate the sedative, the anterograde amnesic, and partly the anticonvulsive effects of diazepam. GABAA receptors containing α2 mediate the anxiolytic actions and to a large degree the myorelaxant effects. GABAA receptors containing α3 and α5 also contribute to benzodiazepines myorelaxant actions, whereas GABAA receptors comprising the α5 subunit were shown to modulate the temporal and spatial memory effects of

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benzodiazepines.[100] Diazepam is not the only drug to target these GABAA receptors. Drugs such as flumazenil also bind to GABAA to induce their effects.

Diazepam appears to act on areas of the limbic system, thalamus, and hypothalamus, inducing anxiolytic effects. Benzodiazepine drugs including diazepam increase the inhibitory processes in the cerebral cortex.

The anticonvulsant properties of diazepam and other benzodiazepines may be in part or entirely due to binding to voltage-dependent sodium channels rather than benzodiazepine receptors. Sustained repetitive firing seems limited by benzodiazepines' effect of slowing recovery of sodium channels from inactivation.

The muscle relaxant properties of diazepam are produced via inhibition of polysynaptic pathways in the spinal cord.

Bioavailability: 76% (64–97%) by oral, 81% (62–98%) rectal

Biological Half-Life

(50 hours); 20–100 hours (36–200 hours for main active metabolite desmethyldiazepam).

EXCIPIENTS PROFILES

Pharmaceutical Excipients

Pharmaceutical excipients are substances, other than the pharmacologically active drug or pro-drug, which are included in the manufacturing process or contained in the finished pharmaceutical product dosage form. Excipients provide enhanced functionality to the pharmaceuticals, aid the innovations in the drug development and help improve patent life as well. Excipients make the products more functional at a lower cost, a benefit much desired by the pharmaceutical industry that is inundated with pressures to reduce costs.

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Excipients play a wide variety of functional roles in pharmaceutical dosage forms. Including,

- Modulating the solubility and bioavailability of active pharmaceutical ingredients.
- Increasing the stability of active ingredients in dosage forms.
- Helping active ingredients maintain preferred polymorphic forms or conformations.
- Maintaining the pH and/or osmolarity of liquid formulations.
- Acting as antioxidents, emulsifying agents, aerosol propellants, tablet binders and tablet disintegrants.
- Preventing aggregation or dissertation (e.g of protein and polysaccharides actives).
- Modulating immunogenic responses of active ingredients (e.g adjunts).

PREFORMULATION STUDIES

Pre-formulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It is the first step in rational development of drug dosage forms of a drug substance. It provides the information required to define the nature of the drug and a frame work for the drug combination with pharmaceutical excipients in dosage form. [91]

Organoleptic properties

The colour, odour and taste of the drugs were studied.

Particle size and shape

Particle size and shape of the drugs were studied by optical microscopic method.

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Melting point

Melting points of the drugs were confirmed by capillary tube method.

Solubility analysis

Solubility is the important parameter for preformulation studies because,

1. It affects the dissolution of the drug.
2. Bioavailability of drug is directly affected by oral administration and also by dissolution.
3. Particle size, shape, surface area may affect the dissolution characteristics of drug hence it should be determined during preformulation.

Method: Weighed quantity of drug was added to the suitable volume of solvent and solubility checked.

Loss on drying (%)

1g of drug was accurately weighed and dried in an oven at 105°C for 3 hours. By gentle sidewise shaking, the sample was distributed at the specified temperature for constant weight. The drug sample was allowed to come to room temperature in desiccators before weighing.

The difference between successive weights should not be more than 0.5mg. The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{W3 - W2}{W2 - W1} X100$$

Where,

W1 – Weight of empty weighing bottle

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W2 – Weight of weighing bottle + sample

W3 – Weight of weighing bottle + dried sample

Drug Excipients Compatibility Study

The drug and the excipients chosen for the formulations were screened for compatibility by physical methods and Fourier Transform Infrared spectroscopic studies.

Chemical compatibility study by FTIR

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drugs, polymers, excipients, drug excipients mixture was subjected to FTIR studies to investigate the drug- excipients interactions. The IR spectra of the test samples were obtained by pressed pellet technique using potassium bromide. [92]

Calibration Curve for Diazepam

100mg of drug was weighed and transferred to a 100ml standard flask and dissolved in ethanol and made up to the volume with distilled water. 10ml of the stock solution was pipetted out into separate 10ml standard flask and made upto the volume using distilled water as solvent. From the resulting solution, dilutions in the range of 2.0 to 10.0 µg/ml of the drug were prepared with distilled water. The absorbance of the solutions was measured at λ_{max} 284nm using UV – Visible spectrophotometer. The calibration curve was then plotted taking concentration (µg/ml) along X-axis and absorbance along Y- axis. [93]

BATCH MANUFACTURING

The manufacturing process consisted in a direct compression. Where, diazepam, lactose, disintegrant and povidone were blended for 15 minutes. Magnesium stearate was then added to the previous blend and mixed for 5 minutes more, and the obtained blend was compressed.

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ANALYTICAL TECHNIQUES

Weight variation

Randomly, twenty tablets were selected after compression and the mean weight was determinated. None of the tablets deviated from the average weight by more than ± 7.5%.

Dissolution

In vitro drug release was performed for diazepam ODT according to the USP30-NF25 "Dissolution procedure" for immediate release dosage forms. A minimum of 6 tablets of each formula were tested. The dissolution of oral disintegrating tablets was executed using USP 30 (apparatus 2) paddle method. Dissolution was carried out in 900 ml of HCl 0.1M medium for 15 minutes. The paddle was rotated at 100 rpm at 37±0.5 ºC.

Samples were filtered through a 0.45µm pore size membrane filter (Millipore Co., USA) and analyzed spectrophotometrically at 284 nm.

Disintegration

In vitro disintegration test was assessed according to the USP30-NF25 requirements. One dosage unit was put in each of the six tubes of the basket. The apparatus was operated, using distilled water as the immersion fluid, maintained at 37°C±2°C. Time for complete disintegration of each tablet, standard deviation and relative standard deviation were calculated.

Hardness

Tablet hardness was determined using the Hardness Tester for 10 tablets of each batch; the average hardness, standard deviation and relative standard variation were reported.

Wetting Time

Five circular tissue paper of 10 cm diameter were placed in a Petri dish. 10 ml of simulated saliva pH (pH 6.8 phosphate buffer) was poured into the tissue paper placed in the Petri dish.

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Few drops of crystal violet solution were added to the Petri dish. A tablet was placed carefully on the surface of the tissue paper. The time required for the solution to reach upper surface of the tablet was noted as the wetting time.(94)

Water Absorption Ratio

The weight of the tablet before keeping in the Petri dish was noted (W2). Fully wetted tablet from the Petri dish was taken and reweighed (W1). (94)

The water absorption ratio can be determined according to the following formula:

$$Water\ Absorption\ Ratio = \frac{W_1 - W_2}{W_2} \times 100$$

QUALITY BY DESIGN TOOLS

Risk Assessment

Risk assessment was used throughout development to identify potentially high risk formulation and process variables and to determine which studies were necessary to increase our knowledge. Each risk assessment was then updated to capture the reduced the level of risk based on our improved product and process understanding. The relative risk that each attribute was ranked as high, medium, or low, as shown in Table 7. Those attributes that could have a high impact on the drug product CQAs warranted further investigation whereas those attributes that had low impact on the drug product CQAs required no further investigation.

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Overview of Relative Risk Ranking System

Low	Broadly acceptable risk. No further investigation is needed.
Medium	Risk is accepted. Further investigation may be needed in order to reduce the risk.
High	Risk is unacceptable. Further investigation is needed to reduce the risk.

This relative risk ranking system was used to assess the risk in the pharmaceutical development of some drug products.

Ishikawa Diagram

The Ishikawa diagram is an important scientific tool used to identify and clarify the causes of an effect of interest. When lead improvement team members construct such a diagram, it allows them to build a visual theory about potential causes and effects that can be used to guide improvement work. Also called fishbone or cause and effect diagram, it can stimulate the formation of hunches worth empirically testing. In addition, the Ishikawa diagram promotes a disciplined use of major categories of potential causes. As a result, rather than allowing people to focus on a few top-of-the-mind areas, it facilitates deeper thinking about possible causation. Finally, it can help the team answer the question of where to begin the process of improvement.

Design of Experiment

For DoE, a two factors three variables (level) (32) factorial was used in first and second steps which requires 9 experiments in each step. In the first step, the two factors X1, type of disintegrant and X2, level of disintegrant are represented by –1, 0, and +1, corresponding to the low, middle and high values respectively.

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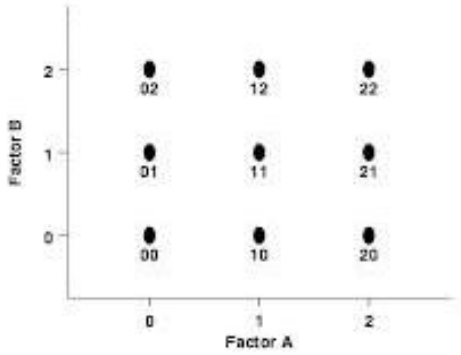

DRUG PRODUCT FORMULATION DEVELOPMENT

Initial risk assessment

In this initial risk assessment for formulation development, the manufacturing process has not been established in detail. The study was conducted in a laboratory scale, using a hydraulic press for the compression step. The use of the hydraulic compression press would allow a better control of the compression force applied as well as the compression time. Therefore, risks were rated assuming a similar behavior between the equipment used in the formulation development and in the manufacturing process development.

Table 12 Initial Risk Assessment of the Formulation Variables

CQA	Formulation Variables				
	Diazepam	**Lactose M80**	**Povidone**	**Disintegrant**	**Magnesium stearate**
Hardness	Low	Low	Medium	Medium	Low
Disintegration	Low	Low	Low	High	Low
Dissolution	High	Low	Medium	High	Medium

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The physical and chemical properties of diazepam have some impact in the CQAs, particularly in dissolution. The drug substance is a BCS class II compound and therefore, it was considered that the diazepam particle size is a critical variable affecting dissolution.

Lactose 80 M, as filler, is not expected to have a decisive influence over the CQAs defined, especially because its grade is defined as 80M which is the most adequate for direct compression. As a consequence, the risk is considered low for all CQAs.

Povidone, as binder, affects directly tablet cohesiveness and breaking force, but can be controlled during compression. Therefore its risk is considered medium for hardness. In a less extension it can also affect dissolution and disintegration, which can be managed by the type and amount of disintegrant. Therefore, both quality attributes have a medium and low risk, respectably.

Regarding the defined CQAs, the disintegrant is considered as a critical variable and was subject of study. Disintegrant level impact the disintegration time and, ultimately, dissolution. Since achieving rapid disintegration is important for an ODT containing a BCS class II compound, the risk is high. Therefore, three disintegrants were studied, sodium starch glycolate, croscarmellose sodium and crospovidone, at different level.

As lubricant, magnesium stearate may have an influence in dissolution since lubrication due to excessive lubricant may retard the drug release. It can also have some impact in the tablet hardness due to over-blending. However this risk is minimized by the use of brittle filler (lactose). Consequently, it is considered a medium risk variable.

The risk assessment also indicates that hardness and disintegration time should be used as the response variables. Additionally, to predict the behavior of the tablet in the mouth, the wetting time was tested. As well, water absorption ratio were tested to understand the mechanism of disintegration of the different disintegrant used.

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Study Design

Formulation development was focused on evaluation of the high risk formulation variables as identified in the initial risk assessment shown in Table 12.

The formulation development was conducted in two studies: the first formulation study was a feasibility study of the compression step and also studied the impact of the binder on the drug product CQAs and the second formulation study was conducted to allow the selection of the disintegrant and it level. Formulation development studies were conducted at laboratory scale.

Feasibility Studies

The first formulation study evaluated the feasibility of the manufacturing process and studied the impact of the binder on the drug product CQAs. In order to understand the properties of the initial formulation and the compression parameters to produce tablets by direct compression, four formulations were prepared with varying the superdisintegrant and the presence of binder as shows Table 13. All four formulations were prepared without the drug substance.

Table 13 – Formulation Code Characterization

Formulation code	Superdisintegrant	Binder
A1	Sodium starch glycolate at 10 %	Povidone
B1	Croscarmellose sodium at 10 %	Povidone
A2	Sodium starch glycolate at 10 %	Absent
B2	Croscarmellose sodium at 10 %	Absent

Crospovidone has some binder properties, therefore the study was performed only in sodium starch glycolate and croscarmellose sodium at 10%, assuming the worst case for both disintegrants.

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All four formulations were tested for two different compression parameters. Table 14 details the equipment and the associated process parameters used in these studies.

Table 14 Equipment and Fixed Process Parameters used in Formulation Development Studies

Process step	Equipment	Process parameters
Blending	V Blender coupled to ERWEKA Rotor AR402	375 revolutions for blending (15 min at 25 rpm)
Lubrication	V Blender coupled to ERWEKA Rotor AR402	125 revolutions for blending (5 min at 25 rpm)
Compression	SPECAC Hydraulic Press	2 tonnes during 10 seconds or 5 tonnes during 5 seconds

Tablets were analyzed regarding hardness, disintegration and wetting time. The compression parameters showing the higher hardness without compromise the disintegration time was selected for the following experiments. The same study was performed for the effect of the presence of the binder in the formulation.

Selection of Disintegrant

To evaluate the influence of the disintegrant and it level a second set of experiments was designed. Therefore, batches differing in the disintegrant type and disintegrant level were prepared. The study is described in detail in Table 15.

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Table 15 Design of the Selection of the Disintegrant Study

Factor	**Level**		
Disintegrant	**-1**	**0**	**1**
Type of Disintegrant	Sodium starch glycolate	Croscarmellose sodium	Crospovidone
Disintegrant level (%)	10	20	30

The superdisintegrants croscarmellose sodium, sodium starch glycolate, crospovidone were challenged at 3 different levels, 10%, 20% and 30%.

The results obtained from de previous study allowed the selection of the compression parameters for this study. Additionally, the presence or absence of the binder in formulation was concluded in the feasibility study. Table 14 details the equipment and the associated process parameters for blending and lubrication.

Tablets were analyzed regarding hardness, disintegration and wetting time. Additionally, it was studied the water absorption capacity for the obtained tablets. The disintegrant showing the lowest disintegration time and good physical properties was selected for the following experiments.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

DRUG PRODUCT FORMULATION DEVELOPMENT

Initial risk assessment

In this initial risk assessment for formulation development, the manufacturing process has not been established in detail. The study was conducted in a laboratory scale, using a hydraulic press for the compression step. The use of the hydraulic compression press would allow a better

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	Diazepam	**Lactose M80**	**Povidone**	**Disintegrant**	**Magnesium stearate**
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As lubricant, magnesium stearate may have an influence in dissolution since lubrication due to excessive lubricant may retard the drug release. It can also have some impact in the tablet hardness due to over-blending. However this risk is minimized by the use of brittle filler (lactose). Consequently, it is considered a medium risk variable.

The risk assessment also indicates that hardness and disintegration time should be used as the response variables. Additionally, to predict the behavior of the tablet in the mouth, the wetting time was tested. As well, water absorption ratio were tested to understand the mechanism of disintegration of the different disintegrant used.

Study Design

Formulation development was focused on evaluation of the high risk formulation variables as identified in the initial risk assessment shown in Table 12.

The formulation development was conducted in two studies: the first formulation study was a feasibility study of the compression step and also studied the impact of the binder on the drug product CQAs and the second formulation study was conducted to allow the selection of the disintegrant and it level. Formulation development studies were conducted at laboratory scale.

Feasibility Studies

The first formulation study evaluated the feasibility of the manufacturing process and studied the impact of the binder on the drug product CQAs. In order to understand the properties of the initial formulation and the compression parameters to produce tablets by direct compression, four formulations were prepared with varying the superdisintegrant and the presence of binder as shows Table 13. All four formulations were prepared without the drug substance.

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Table 13 – Formulation Code Characterization

Formulation code	Superdisintegrant	Binder
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B1	Croscarmellose sodium at 10 %	Povidone
A2	Sodium starch glycolate at 10 %	Absent
B2	Croscarmellose sodium at 10 %	Absent

Crospovidone has some binder properties, therefore the study was performed only in sodium starch glycolate and croscarmellose sodium at 10%, assuming the worst case for both disintegrants.

All four formulations were tested for two different compression parameters. Table 14 details the equipment and the associated process parameters used in these studies.

Table 14 Equipment and Fixed Process Parameters used in Formulation Development Studies

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Compression	SPECAC Hydraulic Press	2 tonnes during 10 seconds or 5 tonnes during 5 seconds

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Tablets were analyzed regarding hardness, disintegration and wetting time. The compression parameters showing the higher hardness without compromise the disintegration time was selected for the following experiments. The same study was performed for the effect of the presence of the binder in the formulation.

Selection of Disintegrant

To evaluate the influence of the disintegrant and it level a second set of experiments was designed. Therefore, batches differing in the disintegrant type and disintegrant level were prepared. The study is described in detail in Table 15.

Table 15 Design of the Selection of the Disintegrant Study

Factor	**Level**		
Disintegrant	**-1**	**0**	**1**
Type of Disintegrant	Sodium starch glycolate	Croscarmellose sodium	Crospovidone
Disintegrant level (%)	10	20	30

The superdisintegrants croscarmellose sodium, sodium starch glycolate, crospovidone were challenged at 3 different levels, 10%, 20% and 30%.

The results obtained from de previous study allowed the selection of the compression parameters for this study. Additionally, the presence or absence of the binder in formulation was concluded in the feasibility study. Table 14 details the equipment and the associated process parameters for blending and lubrication.

Tablets were analyzed regarding hardness, disintegration and wetting time. Additionally, it was studied the water absorption capacity for the obtained tablets. The disintegrant showing the lowest disintegration time and good physical properties was selected for the following experiments.

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MATERIALS AND METHODS

For the Development of diazepam oral disintegrating tablet formula givan below in table No. 1

Table No. 1: Formulation Composition of Diazepam ODT

Ingredient	Function	Quantity (mg)
Diazepam	Active Pharmaceutical Compound	5
Lactose 80 M	Filler	139.0 - 183.0
Povidone	Binder	0 - 5.6
Superdisintegrant	Disintegrant	22 – 66
Magnesium stearate	Lubrificant	4.4

The composition of diazepam ODT. This formulation was composed by Diazepam, filler, a binder, superdisintegrant and a lubricant. Lactose is a widely used excipient and was selected as filler due to its water solubility and acceptable compressibility properties. A direct compression grade of lactose was selected and its amount varied accordingly to the superdisintegrant content. A binder was included in the formulation in a very small amount in order to improve the mechanical properties of the tablets. Povidone was selected due to its acceptable compressibility in a dry from and due to its water solubility. Magnesium stearate which is the most used lubricant was selected due to its good compressibility properties in a relatively low concentration. Moreover, the level provided for each excipient is consistent with previous experience and based on literature. The formulation has a final mass of 220 mg.

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DRUG PRODUCT FORMULATION DEVELOPMENT

Initial risk assessment

The study was conducted in a laboratory scale, using a hydraulic press for the compression step. Data given in table 2.

Table No.2 Initial Risk Assessment of the Formulation Variables

CQA	Formulation Variables				
	Diazepam	**Lactose M80**	**Povidone**	**Disintegrant**	**Magnesium stearate**
Hardness	Low	Low	Medium	Medium	Low
Disintegration	Low	Low	Low	High	Low
Dissolution	High	Low	Medium	High	Medium

Feasibility Studies

In order to understand the properties of the initial formulation and the compression parameters to produce tablets by direct compression, four formulations were prepared with varying the superdisintegrant and the presence of binder as shows Table 03.

Table No. 03 – Formulation Code Characterization

Formulation code	Superdisintegrant	Binder
A1	Sodium starch glycolate at 10 %	Povidone
B1	Croscarmellose sodium at 10 %	Povidone
A2	Sodium starch glycolate at 10 %	Absent
B2	Croscarmellose sodium at 10 %	Absent

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All four formulations were tested for two different compression parameters. Table 04 details the equipment and the associated process parameters used in these studies.

Table 4 Equipment and Fixed Process Parameters used in Formulation Development Studies

Process step	**Equipment**	**Process parameters**
Blending	V Blender coupled to ERWEKA Rotor AR402	375 revolutions for blending (15 min at 25 rpm)
Lubrication	V Blender coupled to ERWEKA Rotor AR402	125 revolutions for blending (5 min at 25 rpm)
Compression	SPECAC Hydraulic Press	2 tonnes during 10 seconds or 5 tonnes during 5 seconds

Selection of Disintegrant

To evaluate the influence of the disintegrant and it level a second set of experiments was designed. Therefore, batches differing in the disintegrant type and disintegrant level were prepared. The study is described in detail in Table 5.

Table No. 05 Design of the Selection of the Disintegrant Study

Factor	**Level**		
Disintegrant	**-1**	**0**	**1**
Type of Disintegrant	Sodium starch glycolate	Croscarmellose sodium	Crospovidone
Disintegrant level (%)	10	20	30

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RESULTS

Preformulation Studies

Physico Chemical Characterization of Diazepam

Diazepam raw material obtained from Fair Point Pharmaceutical, Srinagar was tested as per in house specification and the results are listed in table 06. The drug source is identified and found complying with the specifications.

Table No. 06: Characterization of Diazepam

SNo	Test	Specification	Results
1	Description	White or yellow crystalline powder	A white crystalline powder
2	Loss on drying	4.9 to 5.3% W/W	5.25% W/W
3	Solubility	Very slightly soluble in water, soluble in alcohol, and freely soluble in chloroform	Complies
4	Melting point	131.5 to 134.5 °C	131 to 134 °C

Feasibility Studies

Formulations A1 and B1 were successfully compressed, resulting in flat, white, uniform tablets. The tablets manufactured from formulations A2 and B2 exhibit a weaker consistence due the absence of binder. Table 7 summarizes the results of weight, thickness, diameter and hardness.

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Table No. 7: Mean weight, Thickness, Diameter and Hardness Results of Tablets

Formulation code	Weight[a] (mg)	Thickness[b] (mm)	Diameter[b] (mm)	Hardness[b] (N)
A1	217.1 ± 1.6	1.15 ± 0.02	12.77 ± 0.04	19.4 ± 2.2
A2	213.3 ± 1.9	1.18 ± 0.01	12.12 ± 0.82	7.0 ± 0.7
B1	217.1 ± 2.7	1.14 ± 0.01	13.08 ± 0.01	20.9 ± 1.2
B2	215.1 ± 3.3	1.16 ± 0.02	13.07 ± 0.01	14.8 ± 2.4

The results are mean ± SD of a 10 tablets; b 3 tablets.

Disintegration and Wetting Time

The results of disintegration and wetting time are given in Table 8.

Table No. 08: Disintegration Time and Wetting Time Results of Tablets

Formulation code	Disintegration time (s)	Wetting time (s)
A1	19.8 ± 2.6	92.4 ± 5.7
A2	14.6 ± 2.2	14.4 ± 1.3
B1	30.0 ± 4.6	44.8 ± 4.3
B2	12.8 ± 0.8	13.3 ± 1.5

The results are mean ± SD of 3 tablets.

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Selection of Disintegrant

Table No. 9: DoE Design for the Selection of Disintegrant

Factor	Experiment								
	#1	#2	#3	#4	#5	#6	#7	#8	#9
Type of Disintegrant	SSG	SSG	SSG	CS	CS	CS	CP	CP	CP
Disintegrant level (%)	10	20	30	10	20	30	10	20	30

This results in the manufacturing of 9 batches, according to Table 10, obtained by direct compression. The compression parameters, selected in the previous study, was a force compression of 5 tonnes with a duration of 5 seconds. All the quantities expressed are in mg / tablet.

Table 10: Tablet Formulation

Ingredient (mg)	Formula code								
	A1	A2	A3	B1	B2	B3	C1	C2	C3
Diazepam	5	5	5	5	5	5	5	5	5
Lactose 80 M	183.4	161.4	139.4	183.4	161.4	139.4	183.4	161.4	139.4
Povidone	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2
Sodium starch glycolate	22	44	66	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	22	44	66	-	-	-
Crospovidone	-	-	-	-	-	-	22	44	66
Magnesium stearate	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Total	220	220	220	220	220	220	220	220	220

All formulations were successfully compressed, resulting in flat, white, uniform tablets, showing good consistence. The results of weight, thickness and diameter are given in Table 11. & Figure 01 summarizes the results obtained in hardness test.

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Table 11: Mean Weight, Thickness and Diameter Results of Tablets

Formulation code	Weight[a] (mg)	Thickness[b] (mm)	Diameter[b] (mm)
A1	222.1 ± 1.4	1.18 ± 0.02	13.07 ± 0.02
A2	222.3 ± 1.5	1.22 ± 0.02	13.10 ± 0.04
A3	222.0 ± 1.3	1.23 ± 0.02	13.14 ± 0.05
B1	220.5 ± 1.6	1.23 ± 0.03	13.14 ± 0.02
B2	222.2 ± 2.0	1.25 ± 0.03	13.25 ± 0.03
B3	225.0 ± 1.3	1.23 ± 0.02	13.24 ± 0.05
C1	223.1 ± 1.7	1.25 ± 0.03	13.11 ± 0.02
C2	222.6 ± 2.3	1.38 ± 0.05	13.12 ± 0.03
C3	228.2 ± 1.8	1.46 ± 0.03	13.33 ± 0.11

The results are mean ± SD of a 20 tablets; b 10 tablets.

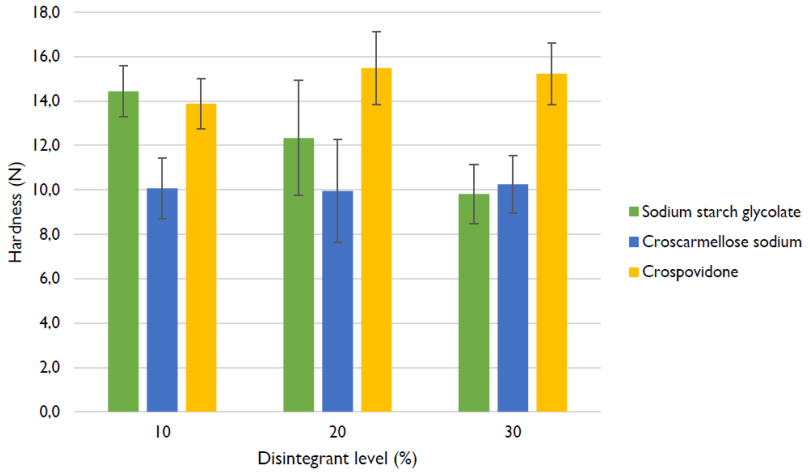

Figure 01 – Hardness results of tablets. The results are mean ± SD of 10 tablets.

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Table 12 summarizes the results obtained for disintegration time, wetting time and water absorption ratio. Figure 02 shows the relation between disintegration time and wetting time.

Table 12: Disintegration Time, Wetting Time and Water Absorption Ratio Results of Tablets

Formulation code	Disintegration time[a] (s)	Wetting time[a] (s)	Water absorption ratio[b] (%)
A1	14.8 ± 2.5	40.5 ± 5.7	131.2 ± 6.4
A2	13.2 ± 1.7	72.8 ± 3.1	235.4 ± 3.1
A3	10.5 ± 1.7	94.7 ± 3.1	370.7 ± 5.9
B1	29.0 ± 3.3	24.2 ± 2.5	108.0 ± 6.1
B2	33.7 ± 2.3	46.9 ± 2.8	185.2 ± 8.2
B3	31.7 ± 2.6	87.9 ± 8.2	253.0 ± 15.1
C1	19.4 ± 1.5	20.6 ± 1.5	61.5 ± 2.1
C2	18.3 ± 1.5	17.2 ± 1.2	91.1 ± 0.5
C3	15.6 ± 2.2	12.3 ± 1.5	103.8 ± 1.4

The results are mean ± SD of a 6 tablets; b 3 tablets.

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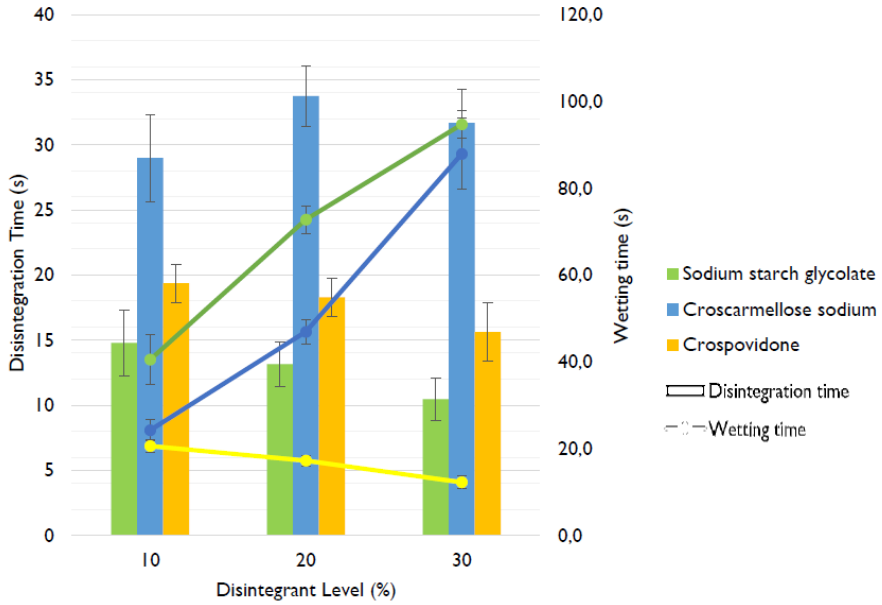

The results are mean ± SD of 6 tablets.

Figure 02 – Disintegration time and wetting time results of tablets

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