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Design of an orally disintegrating tablet formulation containing metoprolol tartrate in the context of quality by design approach

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ABSTRACT: Orally Disintegrating Tablets (ODTs) are solid dosage forms that rapidly disintegrate or dissolve to release the drug upon contact with saliva in the mouth. As these tablets require special attention during formulation design, it is necessary to use advanced control and formulation design techniques to increase the quality. Quality by Design (QbD) was defined as an approach including better scientific understanding of critical process and product attributes, designing controls and tests based on scientific understanding limits during development stage and used to work in an environment for continuous improvement of information obtained during the product lifecycle. The aim of the study was to develop an ODT formulation containing Metoprolol tartrate with appropriate features via QbD approach with the help of artificial intelligence programs to enlight the multivariate relations between critical parameters and quality attributes of on final product and to obtain an optimum formulation. Physical and chemical tests were conducted on tablets prepared by direct compression according to the designated formulation and process variables. Then, experimental data was evaluated with modeling programs use artificial intelligence technique, FormRules V3.32 to understand the relationship between independent input variables and the critical quality attributes; later with INForm V5.1 for optimization. The optimized formula was prepared and according to test results tablets shows compliance with the pharmacopoeia limits. The adoption of QbD approach and usage of artificial intelligence programs has increased the efficiency of the formulation development process with better understanding of the product and process.

KEYWORDS: Artificial intelligence; orally disintegrating tablet; quality by design; metoprolol tartrate.

1. INTRODUCTION

A drug delivery system is a strategic tool for a pharmaceuticals' drug development, life cycle and market growth and was observed to be effective in the drug choice. Increasing patient compliance during drug development is a very demanded approach; therefore, the demand for technologies ensuring this also increased. High budget financial investment, hard work and time are required to develop a chemical compound as a novel drug. Thus, it is mostly aimed to provide increased safety, bioavailability of a drug molecule while maintaining its therapeutic efficacy; recent developments in new drug systems aim for the same concern by designing a dosage form [1, 2]. Another requisition also emerged for the development of easy-to-use dosage forms by many patients with the change of lifestyle [3].

Oral Disintegrating Tablets (ODTs) are solid dosage forms that rapidly disintegrate or dissolve to release the drug immediately upon contact with saliva in the mouth and eliminate the need to chew the tablet or use water during administration. European Pharmacopoeia (EP) states ODTs must disintegrate within 3 minutes when the conventional disintegration test for tablets applied. ODTs were developed for many indications from migraine (because fast onset of action is important) to mental diseases (because patient compliance is important in treating chronic indications such as depression and schizophrenia). ODTs were observed to have significantly higher drug solubility, absorption, bioavailability, and clinic effect compared to traditional solid dosage forms. It also provides the opportunity to contain high amounts of active ingredients. Various methods such as lyophilisation, spray drying and direct compression are used in the manufacture of ODTs [4, 5]. As they require special attention during formulation development, quality control of ODTs is also very important. Therefore, it is necessary to use advanced formulation techniques to increase the quality.

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Metoprolol tartrate (MT) is a selective beta 1- adrenoreceptor blocking active ingredient used in the treatment of continuous hypertension, protection after myocardial infarction, tachycardia, coronary heart disease (preventing angina attack) and coronary failure [6].

The drug manufacturing is complex, starting from formulation development stage to the finished product; this process includes multi-variable interactions between the raw materials and process conditions. Understanding and controlling these interactions is very important for operation capability and finished product quality. Increase in the complexity and difficulty of drug developing and manufacturing, leading to cost increase and loss of time have increased the problems encountered during product registration. The US Food and Drug Administration (FDA) announced the Current Good Manufacturing Practice (cGMP) to the drug industry in 2002 to ensure easier integration to the change in drug development. As part of these developments, the concept of Quality by Design (QbD) was defined as an approach including better scientific understanding of critical process and product attributes, designing controls and tests based on scientific understanding limits during development stage and used to work in an environment for continuous improvement of information obtained during the product life cycle [7].

Focusing on the content of the Common Technical Document (CTD) Module 3.2.P.2 in 2005, The International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) published the Q8 guideline and the concept of QbD came to life with this guideline. An important step in the QbD definition required a distinction between Critical quality attributes (CQAs) of product with high potential to be affected from critical formulation or process variables (CPPs) and non-ritical ones. The ICH Q9 guideline was published to conduct risk assessment and to manage the defined risks in this regard. Later, the ICH Q10 guideline was presented to arrange the quality management systems of drug manufacturers and followed by the Q11 guideline on raw material manufacturing and the Q12 guideline on Lifecycle management [8, 9].

Design of Experiments (DoE) and mathematical models are used in the optimization process under QbD approach. Beside statistical programs, many computer-based systems such as Artificial Neural Network (ANN), Genetic Algorithm (GA) and Fuzzy Logic (FL) help drug developers with an experimental design capability for data required during the development stage of a pharmaceutical product. ANN offers a promising modeling technique, especially for non-linear related data series. GA seeks an optimal holistic result in complex and multi-dimensional research areas according to "strong survives" principle. Neuro Fuzzy Logic (NFL), another artificial intelligence technology can be used to define optimization objectives. NFL is a hybrid technology combining the interpretive power of fuzzy logic with the adaptable learning ability of neural networks to offer a powerful tool to establish interpretable rules from complex and non-linear data [7, 10-12].

The purpose of the study was to develop an oral disintegrating tablet formulation containing the MT using QbD approach and with the help of artificial intelligence programs (FormRules, INForm GEP) based on statistical assessment to gain better knowledge about the effect of formulation and process variables on final product quality attributes which will be very beneficial for R&D departments in pharmaceutical industry. Tablet powder properties were also investigated within the preformulation studies.

2. RESULTS

2.1. Risk assessment and design of experiments

Table 1 shows the CQAs, CPPs and formulation variables determined with risk assessment.

2.2. Examination results of powder mixtures

The prepared powder mixtures and examination results provided in Table 2.

2.3. Results of physical and chemical tests conducted on final product

Table 3 shows tablet formulations prepared using direct compression. The results of physical and chemical tests of compressed tablets are given in Table 4.

According to friability test results, the tablets other than F3, F9, F15, F18, F20, F21, F23 were determined to comply with the pharmacopoeia limits (1%). The hardness values of tablets prepared at low compression force (400 psi) were measured as 0.295-0.676 N/cm2 and the tablets prepared at high force (800 psi) as 0.731-1273 N/cm2. Disintegration durations of tablets were found in the range 16-204 s. All formulations other than F22 complied with the EP limits (< 180 s). There is no pharmacopoeia limit for wetting time and water absorption, however, these taken into consideration as important indicators of disintegration time and of whether the amount of saliva in the mouth will be sufficient for the disintegration; and required to be low.

The disintegration times were in the range 11-136 s; while water absorption values varied in the range 39-163 %. It was observed that all formulations except F11 dissolved at above 85% at 30th minute. As a result of the quantity and content uniformity assay, the MT amount was found as 24.94 mg (RSD 0.36 %) and above 99% with 2% below RSD values.

Table 1. CQAs, CPPs and critical formulation variables of ODT formulations.

Critical Quality Attributes	
Hardness	
Friability	
Wetting Time	
Water Absorption Capacity	
Disintegration Time	
Dissolution Profile	
Formulation Parameters effects Critical Quality Attributes	
Disintegrating Excipient Type	Parteck ® ODT / Sodium starch glycolate + Mannitol
Disintegrating Excipient Amount (mg)	75; 137.5 ; 200 (Determined by preformulation studies)
Filling Material Amount (mg)	147; 84.5; 22 (Determined by preformulation studies)
Lubricant Type	Magnesium stearate / Sodium stearyl fumarate
Lubricant Amount	0.5 % / 1.2 %
Critical Process Parameters	
Compression Pressure (psi)	400; 800 (Determined by preformulation studies)

Table 2. Composition and examination results of powder mixtures.

	Disintegrating Excipient Type*	Disintegrating Excipient Amount (mg)	Avicel Amount (mg)	Lubricant Type**	Lubricant Amount	Hausner Ratio	Carr Index	Angle of Repose	Caking Strength	Mean Caking Strength	Cohesion Index	Flow Stability
P1	1	75	148.75	1	1.25	1.5	33.33	34.09	72.996	2.470	0.05	1.03
P2	1	137.5	86.25	1	1.25	1.42	30	42.2736	3701.87	234.379	0.064	1.08
P3	1	200	23.75	1	1.25	1.36	26.6	31.6075	22.839	1.543	0.047	1.05
P4	1	75	147	2	3	1.53	35	42.2736	38.181	3.215	0.13	1.01
P5	1	137.5	84.5	2	3	1.4	28.57	24.7751	34.904	2.143	0.102	1.03
P6	1	200	22	2	3	1.36	26.66	25.560	4.543	2.258	0.064	1.02
P7	2	75	148.75	1	1.25	1.36	26.67	37.5685	80.782	3.180	0.21	1.03
P8	2	137.5	86.25	1	1.25	1.5	33.33	23.1985	60.747	2.648	0.106	1.09
P9	2	200	23.75	1	1.25	1.25	20	33.69	28.643	1.666	0.036	1.09
P10	2	75	147	2	3	1.5	33.33	39.8055	78.201	4.289	0.1846	1.03
P11	2	137.5	84.5	2	3	1.42	29.99	23.1985	31.415	2.601	0.103	1.03
P12	2	200	22	2	3	1.35	26.66	33.69	8.502	1.768	0.06	1.01

*Disintegrating Type 1: Parteck ODT, Disintegrating Type 2: Sodium Starch Glycolate + Mannitol
**Lubricant Type 1: Magnesium Stearate, Lubricant Type 2: Sodium Stearyl Fumarat

Table 3. Tablet formulations and compression forces.

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Metoprolol tartrate	25	25	25	25	25	25
Parteck ® ODT	75	137.5	200	75	137.5	200
Avicel	148.75	86.25	23.75	148.75	86.25	23.75
MgStearate	1.25	1.25	1.25	1.25	1.25	1.25
Total (mg)	250	250	250	250	250	250
Compression Pressure (psi)	400	400	400	800	800	800
Ingredients (mg)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Metoprolol tartrate	25	25	25	25	25	25
Parteck ® ODT	75	137.5	200	75	137.5	200
Avicel	147	84.5	22	147	84.5	22
Sodium stearyl fumarate	3	3	3	3	3	3
Total (mg)	250	250	250	250	250	250
Compression Pressure (psi)	400	400	400	800	800	800
Ingredients (mg)	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
Metoprolol tartrate	25	25	25	25	25	25
Sodium starch glycolate	7.5	13.75	20	7.5	13.75	20
Mannitol	67.5	123.75	180	67.5	123.75	180
Avicel	148.75	86.25	23.75	148.75	86.25	23.75
MgStearate	1.25	1.25	1.25	1.25	1.25	1.25
Total (mg)	250	250	250	250	250	250
Compression Pressure (psi)	400	400	400	800	800	800
Ingredients (mg)	**F19**	**F20**	**F21**	**F22**	**F23**	**F24**
Metoprolol tartrate	25	25	25	25	25	25
Sodium starch glycolate	7.5	13.75	20	7.5	13.75	20
Mannitol	67.5	123.75	180	67.5	123.75	180
Avicel	147	84.5	22	147	84.5	22
Sodium stearyl fumarate	3	3	3	3	3	3
Total (mg)	250	250	250	250	250	250
Compression Pressure (psi)	400	400	400	800	800	800

Table 4. Results of quality control tests conducted on ODTs.

	Hardness (Kpa)	Friability (%)	Disintegration Time (sec)	Wetting Time (sec)	Water Abs. Capacity (%)
F1	6.7 ± 0.0697	0.1791 ± 0.001	27 ± 0.0663	15.5 ± 0.0889	153.7 ± 0.0575
F2	4.7 ± 0.1578	0.8436 ± 0.0876	20 ± 0.0540	21.8 ± 0.2195	115.25 ± 0.081
F3	4.7 ± 0.1769	1.1985 ± 0.0003	25 ± 0.0645	39 ± 0.1884	85.491 ± 0.1002
F4	12.7 ± 0.0481	0.3233 ± 0.0158	132.6 ± 0.1091	12.5 ± 0.2305	54.493 ± 0.2063
F5	10.7 ± 0.0738	0.5683 ± 0.0211	84 ± 0.0175	33.8 ± 0.2476	46.97 ± 0.2383
F6	10.4 ± 0.0758	0.894 ± 0.0185	59.5 ± 0.0735	46.8 ± 0.2398	44.196 ± 0.1067
F7	4.6± 0.0972	0.4645 ± 0.0872	16 ± 0.0884	11.6 ± 0.2004	139.4 ± 0.0849
F8	4.4 ± 0.1253	0.9973 ± 0.0472	23 ± 0.0916	30.33 ± 0.133	115.471 ± 0.0793
F9	4 ± 0.1438	1.0478 ± 0.1137	27 ± 0.1425	75.8 ± 0.1527	83.538 ± 0.1822
F10	10.3 ± 0.0709	0.358 ± 0.0175	147.6 ± 0.1213	25.6 ± 0.1571	58.613 ± 0.1035
F11	10.5 ± 0.0747	0.4493 ± 0.0523	112.5 ± 0.1272	32.5 ± 0.1904	39.021 ± 0.1421
F12	12.3 ± 0.0897	0.931 ± 0.1171	94.5 ± 0.0314	91.5 ± 0.1643	64.96 ± 0.1849
F13	4.2 ± 0.0916	0.3822 ± 0.0962	26 ± 0.0544	13.1 ± 0.1118	163.973 ± 0.1615
F14	2.9 ± 0.1314	0.9028 ± 0.0025	25 ± 0.0738	27.5 ± 0.1254	133.838 ± 0.1054
F15	3.8 ± 0.0466	1.6028 ± 0.0426	36 ± 0.0609	88.3 ± 0.212	136.4 ± 0.054
F16	9.2 ± 0.0137	0.2781 ± 0.0047	137.5 ± 0.0074	15.6 ± 0.1835	80.563 ± 0.0724
F17	8.3 ± 0.1868	0.6385 ± 0.0524	103 ± 0.1098	21.1 ± 0.3265	43.44 ± 0.1624
F18	9.2 ± 0.0765	1.3158 ± 0.0052	99 ± 0.0234	81.1 ± 0.1452	69.885 ± 0.065
F19	2.9 ± 0.0979	0.8534 ± 0.0326	19 ± 0.0916	13.1 ± 0.1217	160.72 ± 0.0735
F20	4 ± 0.159	1.4373 ± 0.0094	38 ± 0.0584	30.1 ± 0.1175	122.823 ± 0.0884
F21	3.6 ± 0.0718	1.46 ± 0.0589	38 ± 0.1342	131.1 ± 0.1401	133.35 ± 0.0477
F22	8 ± 0.0468	0.4821 ± 0.0355	204 ± 0.0971	17.1 ± 0.213	51.91 ± 0.2261
F23	7.3 ± 0.0361	1.363 ± 0.1059	110 ± 0.0287	32.5 ± 0.1479	45.545 ± 0.1553
F24	9.05 ± 0.1889	0.9908 ± 0.114	120 ± 0.0585	35.3 ± 0.2311	49.358 ± 0.2099

2.4. Evaluation of the experimental data by NFL modelling

R^2 and f- ratio values for output models are given in Table 5, since these values were low for drug release; model was not used for this output.

Table 5. R^2 and f- ratio values for outputs in Neuro-fuzzy and GEP modelling.

Quality Attributes	Neuro-fuzzy		GEP	
	R^2	f-ratio	R^2	f-ratio
Hardness	97.34	56.92	97.43	16.06
Friability	95.08	14.85	92.86	5.48
Disintegration Time	96.70	45.55	96.21	8.24
Wetting Time	66.67	13.33	85.39	1.73
Water Abs. Capacity	98.74	34.32	95.65	8.95
Dissolution rate	5.18	0.57	73.10	1.05

As seen in Table 6, significant rules with confidence levels above 0.90 were created for the trained model. In formulations using sodium starch glycolate, low friability is observed in tablets where the amount of avicel kept high and sodium starch glycolate and mannitol constitute 50% of the total tablet weight. The wetting duration decreases if Avicel amount in formulations is increased. Regardless of disintegrating excipient type, at low compression forces, low disintegration duration is observed if the amount of disintegrating excipient is kept low and Avicel amount is increased. On the other hand, in tablets compressed at high force, the disintegration time is high if Avicel amount is high and disintegrating excipient amount is low. As seen in experimental data, Avicel also shows disintegrant feature at low compression forces. In tablets contain Sodium starch glycolate, water absorption capacity shall increase if Avicel is increased at low compression force. Using high amount Parteck® ODT and low amount Avicel decreases water absorption capacity, regardless of lubricant amount.

2.5. Evaluation of the experimental data by GEP modelling

Within the optimisation studies, an adequate model was created by InForm V5 GEP, R2 and f- ratio values for outputs are given in Table 5. GEP model was also not used for drug release. The optimized formula, suggested to be the best; a total weight of 163 mg tablet, containing 25 mg of MT, 60 mg Parteck® ODT, 76.46

mg Avicel and 1.95 mg Sodium stearyl fumarate compressed with 408 psi. The formula was tested to prove the suitability and the results (4.3 kPa hardness, 0.78 % friability and 16 s disintegration time) showed compliance with estimated attributes.

Table 6. Significant rules created by neuro-fuzzy model.

Rules for formulations using Parteck		*
Avicel Amount is LOW, Disintegrating Exp.Amount is HIGH	Friability is LOW	(1.00)
Compression Pressure is LOW, Avicel Amount is HIGH, Disintegrating Exp.Amount is HIGH	Water Abs. Capacity is HIGH	(1.00)
Avicel Amount is HIGH, Disintegrating Exp.Amount is LOW	Friability is LOW	(1.00)
Rules for formulation using Sodium Starch Glycolate		
Avicel Amount is HIGH, Disintegrating Exp.Amount is LOW	Friability is LOW	(1.00)
Avicel Amount is LOW, Disintegrating Exp.Amount is HIGH	Friability is LOW	(1.00)
Compression Pressure is LOW, Avicel Amount is HIGH, Disintegrating Exp.Amount is LOW	Water Abs. Capacity is HIGH	(1.00)
Compression Pressure is HIGH, Avicel Amount is LOW, Disintegrating Exp.Amount is LOW	Water Abs. Capacity is LOW	(1.00)
Compression Pressure is LOW, Avicel Amount is LOW, Disintegrating Exp.Amount is LOW	Water Abs. Capacity is LOW	(1.00)
Rules for formulation using both Parteck and Sodium Starch Glycolate		
Compression Pressure is LOW, Disintegrating Exp.Amount is LOW, Avicel Amount is HIGH	Disintegration time is LOW	(1.00)
Compression Pressure is LOW, Disintegrating Exp.Amount is HIGH, Avicel Amount is LOW	Disintegration time is LOW	(1.00)
Compression Pressure is HIGH, Disintegrating Exp.Amount is LOW, Avicel Amount is HIGH	Disintegration time is HIGH	(0.92)

Confidence level of the rule.

3. DISCUSSION

When developing a new formulation or process it is important to gain knowledge on multivariable and complex relations between quality attributes and critical parameters. Since, it is overwhelming to search the effect of each variable to quality deciding which variable is critical which is not with risk assessment and creating robust experimental design is important while developing a formulation as established in ICH guidelines.

In this study, main factors of QbD such as risk-based design of experiments, observing the multivariate relations between different variables which have critical impact on product quality and optimization were applied while formulation development. The quality design study were conducted in accordance with previous studies which use artificial neural network with modelling the experimental knowledge [14 - 17]; in this study GEP modelling and Neuro-fuzzy modelling were used together to develop a formulation. Neuro-fuzzy model was very useful in defining the relations between formulation and process variables and CQAs. However, optimization is not possible with this program. To make optimization the experimental knowledge area was also assessed with the InForm GEP program using genetic algorithms. As result of the optimization, an ODT formulation compliant with the limits and showing the required attributes was obtained with a tablet weight lower than the tablet weight kept constant in the experimental studies. The amount of raw materials used in the tablets was thus reduced and profitability was achieved through cost reduction in accordance with the aims of QbD.

The flow attribute, size and morphology of powders are very important in the formulation stage and may impact content uniformity, homogeneity and dissolution rate of the formulation. Within the scope of the study, examining the powder flow properties can be also considered useful in formulating solid dosage forms and eliminating batch differences in industrial scale manufacturing with delivering knowledge that increase robustness of production process. The cohesion index is measured by exerting force against a powder flow and a useful quality control method when attributes of the powder (formulation, powder dimension distribution, particle shape etc.) change. Also, storage conditions and the test medium may change the agglomeration inclination of the powder. Changes in the cohesion may weaken conditions such as filling operations and may impact manufacturing by affecting product quality. The formulations prepared in the study were considered as independent from the flow rate, as the cohesion index values of all formulations are low; and powders show free flow.

Powder flow stability gives information about the flow resistance of the powder. A flow stability value higher than 1 and increased compression value indicates that the powder is more resistant against flow at high rates. If the compression coefficient decreases with increasing rate, then it means that the powder becomes more flied at increased rate. The powder flow stability tests measure the suitability of powder to various transmission rates or to the variability of flow rate attributes from one batch to the other provide insight on the wear characteristics of the powder. It may be necessary to transmit the powder at a certain rate in order to meet the required volume for the product.

Caking is the measure of aggregate formation capacity of powders depending on waiting. The caking tendency depends on cohesiveness and usually a permanent cake forms when operating with cohesive powder. The resistance of the cake depends on many factors such as the stackability efficacy, inter-particle interactions and moisture content [18]. Understanding the agglomeration trend of a powder is important as powders shall be stored in tanks or silos or carried at one point during the manufacture. A powder forms cake easily cannot be taken from a tank as required. According to findings, powder mixtures of formulations, except for the F 2-5 shows low caking tendency. As the formed cakes are weak, the mean cake resistance is also low. Although some formulations have high mean caking and cohesion values, the powders have shown suitable smooth flow at various rates if stored under suitable conditions. Therefore, all formulations were used in the study without elimination.

4. CONCLUSION

DoE is a technique to generate required information from minimum amount of experiment with the help of risk assessment. In addition to understanding how one particular parameter affects product quality, interactions between different parameters could be identified in the limit of experimental design by statistical and artificial intelligence modelling methods such as ANN, GAs and Fuzzy logic that widely used for the purpose of ensuring product quality and helping product development. In studies using such programs as standalone or simultaneously, it was shown these programs were useful in terms of achieving successful results and understanding the formulation, in order to achieve scale-up, reduce the amount of experiments or to get results that were not tried. In this study, powder flow properties examined and with quality control test experimental knowledge area was created. Later, these results were used to obtain optimum formula and compression force with the help of GEP modelling technique while establishing the effect of parameters on critical quality attributes. Adopting Qbd approach and using artificial intelligence programs in the study, to develop an ODT formulation showing suitable attributes and assure product quality, has improved efficiency of the developing stage through increase product and in-process knowledge.

5. MATERIALS AND METHODS

5.1. Materials

Metoprolol tartrate (Sun Pharma, India), Parteck® ODT (Merck Co, Germany), Avicel PH 101 (FMC Biopolymer, Newark, USA), Magnesium stearate (FACI, Genoa, Italy), Sodium starch glycolate (DFE Pharma, Germany), Mannitol (Merck Co, Germany), Sodium stearyl fumarate (SPI Pharma, USA), NaH2PO4.2H2O (Merck), NaOH (Merck).

5.2. Design of Experiments (DoE)

DoE is an organized method that determines factors, which affect process outputs. Process characterization approach contains three key steps. The first step is the risk analysis of parameters specified for process characterization. Secondly, experiments to be conducted suitable for understanding and determining the design area are determined using DoE. Thirdly, the studies are realized and their results are analyzed and the importance of the parameters used is creating the design. It is not feasible to use DoE for all variables. Therefore, variables assigned with low to high-risk values during the evaluations are kept constant in the feasibility studies or taking into consideration previous studies. High-risk variables are evaluated using DoE and the process is thus understood [7, 16]. In this study, the crtitical parameters and tablet quality attributes were evaluated using Risk Ranking and Failure Mode Effects Analysis (FMEA) and in the light of the results, the formulations were determined to create the experimental data [19-21].

5.3. Examining powder mixture attributes

In the study, the powders of tablets to be pressed in the study were prepared according to the determined formulations; and first, values were examined such as the dynamic angle of repose, bulk density, tapped density, Carr Index and Hausner Ratio in order to examine the flow attributes and compressibility [22, 23]. Later, the caking, cohesion and flow stability attributes of the powder mixtures were examined with the Powder Flow Analyzer (Stable Micro Systems) device.

5.3.1. Examining powder flow attributes using the powder flow analyzer

The Powder Flow Analyzer (PFA) can conduct precise measurement to determine the flow attributes of dry and wet powder materials. A precise force transformer on the device allows for viewing reactive forces arising from the displacement of the samples. Powder flow attributes were not considered as critical parameters in this study and were conducted as a preformulation study and in order to obtain forecasting in the scale-up studies.

Cohesion Index: Cohesion is the tendency of particles to reunite and agglomerate. PFA measures this characteristic attribute by lifting the powder with the help of a blade. Powder with higher cohesion shall exert less pressure on the container at it shall stick more to the blade and to itself.

Flow stability: Flow attributes of powders are varied by increasing and decreasing the flow rate. Some powders may show greater resistance against increasing the flow rate, while others may flow more easily. In measuring The Powder Flow Speed Dependency (PSFD) characteristic, the work required to lift a blade with increasing speed from the powder was calculated. The stability assessment of the flow is conducted by comparing the power required at the start with the power required at the end of the experiment.

Caking: A pre-determined force (usually 750 g) was applied to a powder mixture at a measured height, when the required force is reached the height of the caked powder is measured. In the last cycle the target force is reached, the blade compresses the powder and ensures that cake is created at the base of the device container then the cake height are recorded to evaluate the powder compression and settlement. A powder with high inclination for caking shall shows great decrease in colon height and large increase in the cake height. At the end of the cycle the force required to cut the cake was measured and recorded as cake power (resistance); the average cake force is the average power used to split the cake into grams [13].

5.4. Preparation and compression of tablets

Compounds were weighed appropriately then mixed (except lubricant) in the cubic mixer for 15 minutes. The mixture was sifted through a 700-micron sieve. Magnesium stearate sieved through a 700-micron sieve was added to the sifted mixture and further mixed for 5 minutes in the cubic mixer. 250 mg of the prepared mixture were weighed, and the tablets were formed in the single punch tablet compression machine (Yeniyurt, Turkey).

5.5. Physical and chemical tests conducted on tablets

Tablets were evaluated by quality control tests with calculation of standard deviation (SD) and relative standard deviation (RSD) values.

5.5.1. Friability (%)

20 tablets from each formulation were taken, weighed precisely, and placed in the friabilator (Aymes), the test conducted at 25 rpm for 4 minutes, and % weight loss were calculated after weighing the tablets again.

5.5.2. Hardness

10 tablets of each formulation were prepared. The fracture strength of the tablets was measured in Kilopascal (kpa) by the hardness tester (Sotax).

2.5.3. Wetting time and water absorption capacity

A two-folded, thin tissue paper (Internal Diameter = 6.5 cm) was immersed in distilled water in a small petri dish (6 ml). The total wetting time of 6 tablets from each formulation with placing on the paper was measured. Later, by weighing the wetted tablet, the amount of water absorption was calculated by the equation given in Eq. 1.

$$R = 100\ (Wa - Wb)/\ Wb \qquad \text{(Eq. 1)}$$

Where, Wb: Tablet weight before water intake, Wa: Tablet weight after water intake [10, 24].

2.5.4. Disintegration time

The test was carried out in 900 mL distilled water in accordance with the EP. One tablet was placed in 6 tubes on test apparatus entering the dispersion medium and one disc was added to each tube. Dispersion times when no mass stands were measured at each batch [10, 25].

2.5.5. In vitro dissolution test

In vitro dissolution studies were performed using the USP Pallet method. As the dissolution medium, 900 ml of a pH 6.8 phosphate buffer solution maintained at 37 ± 0.5 °C was used. At a specified period, 5 ml of the sample were removed from the dissolution medium, and an equal volume of fresh solvent (37°C) was added after each sample was taken. The dissolved drug amount of sample was determined spectrophotometrically at 221 nm. Then, the cumulative percentage of drug release was calculated [10, 26, 27].

5.6. Assessment of data using neuro-fuzzy logic

In accordance with the quality test results of tablets, FormRules V3.32 was used to understand the relations between the critical process and formulation variables and the pre-determined CQAs. FormRules V3.32 is a data mining software package created by Intelligensys Ltd. using NFL as its basic technology. A series of models were tried for each attribute in order to see which suits the data better and then the model is improved. After the training, the statistical properties, training data, training log and the rules created according to the model can be examined. The rules establish the relations are given in the form as follows:

IF "A" is HIGH, THEN "B" is HIGH. (1. 00)

IF "A" is HIGH, THEN "B" is LOW. (1. 00)

Here "B" can be LOW or HIGH. The number in the brackets indicates the confidence level.

The model statistics with ANOVA (ANalysis Of VAriance) indicates how good the models are and a training set with higher R^2 indicates that more models captured variation in the data and a value greater than 70%, supported by an f-ratio greater than 4, is considered as suitable [11, 12, 15].

5.7. Data assessment using genetic algorithm

INForm V5.1 is a program learning from the data provided using neural networks and indicating what could happen if the component quantity or the operating conditions changes in the given range "if tried". At INForm software package, the task of creating a central model is performed by the ANN component with various backpropagation algorithm and genetic algorithm, fuzzy logic and trained models, also evaluated by ANOVA statistics as explained, used for optimization.

After a model was created from experimental data, the program was again used for optimization to determine the attributes we are trying to obtain and allows us to see which component and operating conditions in our model reaches these, also to build multivariate and multi-level relationship models which is difficult to determine by one-factor-at-a-time approaches [11, 12, 15].

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