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Formulation and Optimization of Fast Dissolving Tablets Containing Sodium Butyrate: Enhancing Oral Delivery Efficiency

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Abstract

Drugs that do not dissolve well or are difficult for the body to absorb can be administered more efficiently with the use of fast dissolving tablets (FDTs), which are becoming more and more common. The goal of this work was to optimize and produce FDTs using sodium butyrate, which is known to be beneficial for several systemic illnesses and intestinal ailments. Creating this FDT was intended to increase the effectiveness of sodium butyrate when taken orally. To do this, a methodical approach was used to refine the formulation of Sodium Butyrate FDTs, utilizing several excipients such as β-cyclodextrin and crospovidone. These components were selected to enhance the solubility, rapid release, and general stability of sodium butyrate. The research included experimental techniques including factorial design, Response Surface Methodology (RSM) to carefully identify and optimize variables such as disintegrants, binders, and superdisintegrants. The effects of these variables on the tablet's physical and chemical characteristics, drug release profile, and disintegration time were examined. To compare the dissolved properties of the improved FDTs with ordinary tablets, in vitro dissolving tests were conducted. The improved sodium butyrate FDTs dissolved considerably more quickly, as demonstrated by the findings, assuring higher bioavailability and faster drug release.

Key words: Sodium Butyrate, Crospovidone, β-cyclodextrine, Fast Dissolving tablet.

Introduction

The potential of fast dissolving tablets (FDTs) to increase patient compliance and improve medication delivery efficiency-especially for drugs with low solubility and bioavailability-has drawn a lot of interest in pharmaceutical research and development. Short-chain fatty acid sodium butyrate has shown promise as a medicinal agent with a range of uses in the management of inflammatory diseases, systemic illnesses, and gastrointestinal problems (Seager *et al*,2017). But its poor oral absorption and low water solubility frequently restrict its effectiveness(Parkash *et al*, 2019; Deepika *et al*,2019). To overcome these obstacles, the development of sodium butyrate fast-dissolving tablet formulations offers a viable means of increasing the effectiveness of the drug's oral distribution (Perrie *et al*,2017; Rades *et al*,2017)). Fast dissolving tablets that

include sodium butyrate provide a number of benefits, including enhanced absorption and bioavailability due to the tablet's quick disintegration and dissolution in the oral cavity (Yin *et al,* 2018; Song *et al,*2018).

This study aims to optimize drug solubility, dissolution rate, and overall oral delivery efficiency of fast-dissolving tablets containing sodium butyrate and excipients such as β-cyclodextrin and Crospovidone, Microcrystalline cellulose, Sodium Saccharin, Mg. Stearate, and Talc by methodically selecting and optimizing excipients.8-9 (Kumari *et al,* 2021;Bhargavi*et al,*2021).Factors such as disintegrants, binders, and superdisintegrants will be thoroughly analyzed and modified utilizing experimental design techniques to get the required drug release profile and tablet properties (Bradoo and Poojary, 2019;Kulu*et at,* 2017). Factors such as binders, superdisintegrants, and disintegrants will be thoroughly assessed and adjusted via the use of experimental design techniques to get the intended drug release profile and tablet properties(Rane*et al,*2020). The chemical and physical characteristics of the improved formulation were also assessed by comprehensive characterization experiments, which included Formulation design (Design Expert). Furthermore, in vitro dissolving investigations will be conducted to contrast the dissolution characteristics of the recently created tablets with those of traditional tablets (Madan *et al,*2018). This investigation aims to contribute to the advancement and elucidation of Sodium Butyrate fast-dissolving tablets, providing a viable means of enhancing their oral delivery effectiveness and therapeutic feasibility. The developed details may be able to help with comprehending consistency and clinical outcomes in the treatment of many gastrointestinal and systemic problems by overcoming the obstacles associated with its poor solubility and bioavailability (Banker and Anderson, 2013;Schussele *et al,*2013).

Materials and methods

Materials

Sodium butyrate salt and all ingredients β-cyclodextrin, Crospovidone, Microcrystalline cellulose, Sodium Saccharin, Mg. Stearate and Talc were collected from CDH chemicals PVT LTD, New Delhi.

Methods

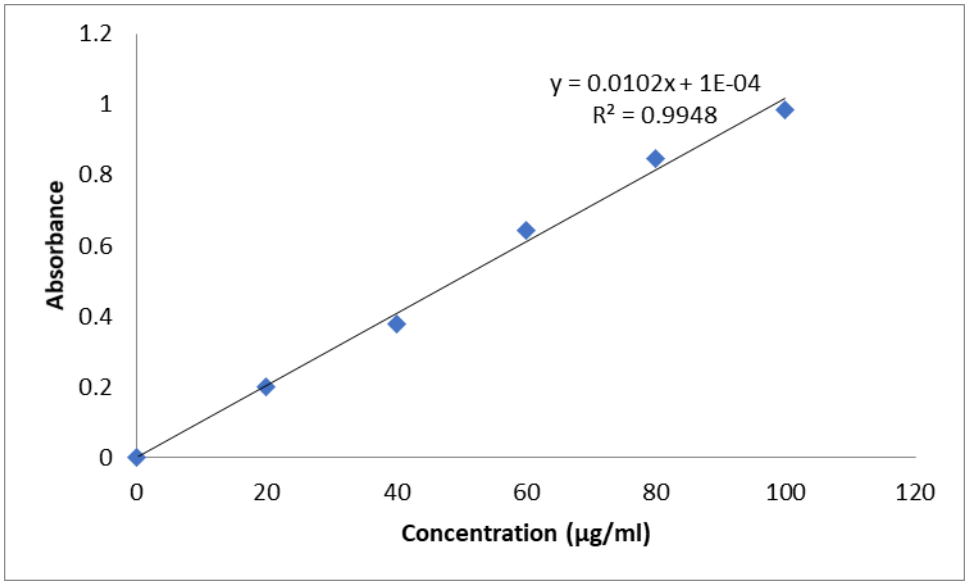
Calibration curve of sodium butyrate

Dissolving 50 mg sodium butyrate in 100 ml water produced a stock solution.The prepared stock solution was utilized to withdraw 10 mL, which was then diluted with water to achieverequired volume (100ml). Calibration curve was produced by diluting stock sample to provide different concentrations between 20 and 100 µg/ml. The wavelength used for the absorbance measurement was 206 nm. In calibration curve all samples were analysed at 206 nm, results of all samples in the term of absorbance of various strength was recorded (Table 1). The standard curve for sodium butyrate is seen in figure 1.

Table No 1: Standard graph of sodium butyrate in distilled water

Sr. No.	Concentration (µg/mL)	Absorbance (206 nm)
1	0	0
2	20	0.201
3	40	0.379
4	60	0.642
5	80	0.845
6	100	0.985

Fig 1: Standard graph of sodium butyrate



Characterization of powder

The powdered sodium butyrate, which has a variety of physical and micromeritic characteristics, is physiologically potent. The powdered sodium butyrate was heterogeneous due to the random interspersion of air gaps between distinct particles of varying sizes and shapes. Each formulation underwent triplicate measurements, results obtained were recorded forensuring robust statistical representation of data (Khan *et al*, 2017).

Determination of angle of repose study

To assess flow properties of fully blended massof components within batches, angle of repose studywas conducted by utilizing required height method, providing insights into their flow characteristics. The well mixed sample, weighing about 10 grams, was progressively added to the funnel wall until the bottom of the funnel was contacted by the tip of the created pile (Bolton *et al*,2021; Kaushik *et al*,2019). Powder's flow characteristics was calculated by using

Tan θ (angle of repose**) =**height of the pile/average radius of the powder cone

Bulk density

Around 25G ofpowderwas passed by a glass funnel into a graduated cylinder (capacity 100ml) for precise determination of both the bulk densities (BD) of sodium butyrate individually and entire powdered mixture as a whole. The samples' original volumes were recorded (Reddy and Setty, 2018; Marshall *et al*,2016)).The bulk density was subsequently computed employing formula Bulk Density= Mass/Volume,

Tapped density

By applying a glass funnel to gently pour 25G sample combination in 100 ml cylinder (graduated), sodium butyrate loaded tapped densities (TD) and entire constituent blend were determined. Once a stable volume was achieved, the cylinder underwent two tapping motions to settle the contents, and resulting average value for each formulation was meticulously documented (Fu *et al*,2016). Following tapping to settle sample, final volume was meticulously recorded, enabling subsequent calculation of tapped density through designated formula.

Tapped Density= wt. of the powder in gm/ volume occupied by the powder after tapping in millilitre

Compressibility study of powder

Compressibility (Carr's) index serves as a valuable experiential reference, offering insights intocompactibility of powdered materials. By contrasting bulk and tapped densities of powdered constituents, it was possible to calculate the compressibility of both the sodium butyrate and the overall combination. Equation provided was used to compute the % compressibility for each formulation.

Carr’s index=tapped density of powder-bulk density of powder/tapped density of powder×100

Hausner’s ratio

Moreover, it demonstrates the compression phenomenon observed in both sodium butyrate and overall component powder mixture, calculated utilizing formula from equation 20, likely influenced by vibrations from feed hopper.Better flowability of the powdered material is indicated by a lower Hausner's ratio, whereas poorer flowability is indicated by a larger Hausner's ratio.

Hausner’s ratio=TD/BD

Optimization of Formulation Using 3^2 Factorial Design (FD)

Experimental Design

We utilized trial version 11.0 of Design Expert software to optimize the studies of generated batches employing a design response surface methodology. With the help of this method, we were able to assess the impact of several formulation elements methodically. 9 trial runs were carried out by us in total. In this investigation, the concentrations of cyclodextrin (X2) and cross povidone (X1) were our independent factors, while the hardness (Y1), friability (Y2), and disintegration time (Y3) were our dependent variables.

Finding out how these answers vary when the values of the two chosen variables are changed was the aim of this investigation.

Generation of polynomial equations

In current optimization investigation, RSM (response surfacymethodology) along with Design Expert software Trial version 11.0 were employed to perform a series of calculations. Multiple Linear Regression Analysis (MLRA) was used to build polynomial models with interactions for each response variable.

Statistical treatment

Minimum P< 0.05 was chosen as the statistical significance cut-off point, and statistical analytic techniques-specifically, ANOVA-were employed using Design Expert software version 11.0 to investigate the impact of independent factors on answers.

Generation of 3D response surface plots

We produced three-dimensional graphs that show how the response surface varies to visualize the responses that we measured. These plots are useful instruments to investigate the simultaneous effects of two variables on a response. They offer a visual depiction of the ways in which independent factors affect the answers.

Preparation of Sodium ButyrateFast-Dissolving tablet (FDT)

Sodium butyrate dispersible tablets were individually prepared using a direct compression method with geometrical dilution mixture, incorporating diverse ingredients such as disintegrating agents, talc, and others. The process was executed utilizing Punching machines, specifically Innovative model No. ITCM001 (Refer to Table No.1 for details).

These formulations were denoted by SBF1 to SBF-9. To ensure consistency, each component was put through a mesh sieve (number 120) and then combined using the geometrical dilution method. Because powder combinations had excellent packing and flow qualities, they were crushed straight from the source (Kaushik *et al*,2019).

Table No.2.Composition of sodium butyrate fast-dissolving tablets

INGREDIENTS (mg/tab)	**SBFDT1**	**SBFDT2**	**SBFDT3**	**SBFDT4**	**SBFDT5**	**SBFDT6**	**SBFDT7**	**SBFDT8**	**SBFDT9**
Sodium butyrate	100	100	100	100	100	100	100	100	100
β-cyclodextrin	100	75	50	100	75	50	100	75	50

Crospovidone	30	30	30	25	25	25	20	20	20
Microcrystalline cellulose	60	75	85	55	80	105	60	85	110
Sod. Saccharin	10	10	10	10	10	10	10	10	10
Mg. Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
TOTAL	310	300	300	300	300	300	300	300	300

Evaluation of Sodium Butyrate FDT

Average weight (mg)

Twenty tablets have been chosen at random from individually batch and weighed separately on an electronic precision balance for assessing weight variation (Citizen, Mumbai). The level of variance was then ascertained by comparing the weights of each tablet with the average weight.

Hardness (kg/cm2)

The tablets' hardness was measured using the Monsanto hardness tester for each formulation; an average was obtained from three different readings.

Friability (%)

The assessment of tablet friability adhered to the guidelines outlined in the United States Pharmacopeia (USP), ensuring rigorous testing standards were met.The percentage of friability was ascertained by reweighing a sample of 6.5 grams of tablets that had been put in the Roch friability test equipment and rotated 100 times(Fu et al, 2016).

Friability (%)= initially weight of tablet− finally weight of tablet/initially weight of tablets × 100

Disintegration time (Min)

The in vitro disintegration time for each formulation was recorded using a USP tablet disintegration test device.

Drug Dissolution (*In-vitro*) study

Hydrochloric acid (0.1 N) in aentire volume of 900 mL was utilized as dissolve medium for the in-vitro dissolving experiment.Throughout entire experiment, the temperature of medium was diligently controlled and upheld at 37 ± 0.5 °C, ensuring consistency and accuracy in the experimental conditions.Furthermore, the dissolving basket was programmed to spin at 100 revolutions per minute (rpm). A sample of a pill was gathered and put inside the container. At intervals of two minutes, a volume of five milliliters was removed from the sample, and an equal volume was then added using brand-new 0.1NHydrochloric acid.After stipulated interval, all samples were filtered and recorded the absorbance using a UV/visible spectrophotometer, meticulously set

to operate at a specific wavelength of 206 nm. Prior to analysis, the samples underwent filtration to ensure clarity and precision in the results.

Stability Study

In accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) criteria, the stability research was conducted.Each formulation was securely stored in aluminum packaging laminated with polyethylene for duration of six months. Humidity chambers were utilized, maintaining conditions at both ambient temperature and accelerated settings as specified. At designated intermissions of 0D, 1M, 2 M, 3M, and 6M, samples were carefully extracted for analysis, ensuring a comprehensive assessment of formulations' stability over time.The samples underwent evaluation for physical characteristics, including color, alongside assessment of drug content. The initial medication concentrations that provided the shelf life (t90), degradation rate constant (Kcal), and two-year shelf life (Int_{cal}) were determined.

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Results and Discussion

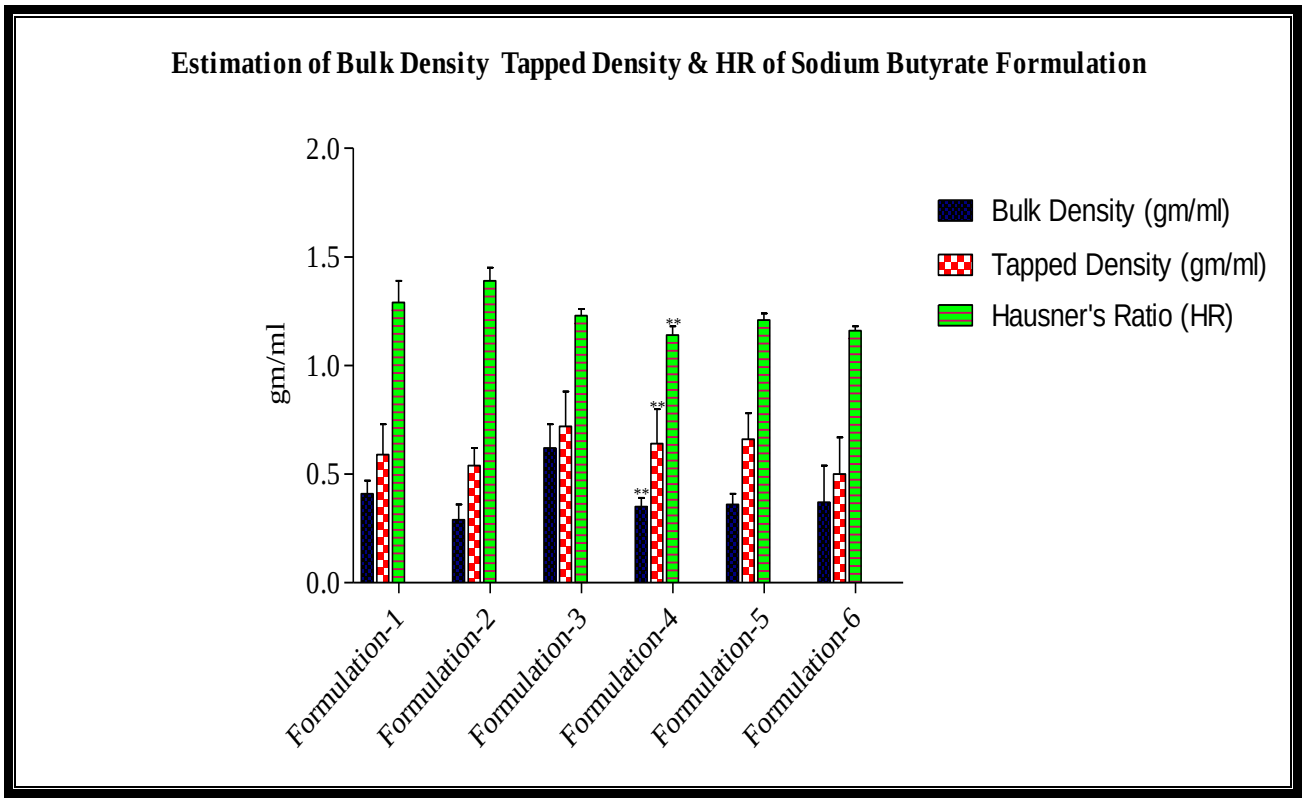
Calibration curve of sodium butyrate in dist. Water

The results obtained from figure no.1 calibration of sodium butyrate in distilled water, the standard curve equation is y = 0.0102x + 1E-04 and the value of Regression Coefficient ($R^{2)}$ is obtained 0.9948.

Micrometrics study of powder

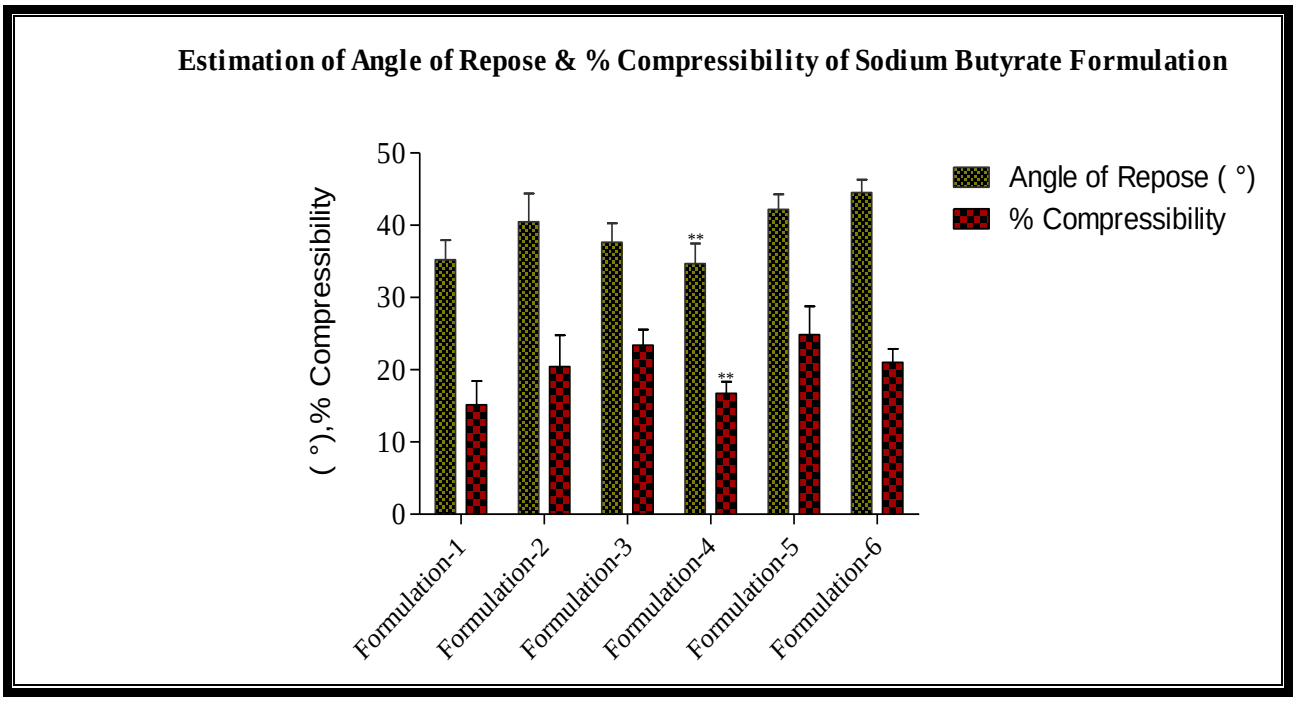
All micrometric behaviour of granules were outlined in Table 3.A measured angle of repose below 45˚ indicates favourable flow behaviour of the granules, suggesting good flow characteristics.Results for bulk density and tapped density of all batches were observed below 0.62 and 0.72. Superdisintegrants inclinereduce bulk density since they often have lower densities than other tablet excipients. Furthermore, their existence can increase interparticle void space, which reduces bulk density. Superdisintegrants may also reduce tapped density by promoting tablet breakdown, resulting in a looser packed structure.The optimized batch exhibited a Hausner's ratio of 1.148, indicating favourable flow characteristics. The % compressibility of all batches was found to be in the range of 15 – 25 % respectively. The average weight and friability of all formulations was fewer than 317 mg and 0.72% respectively.Superdisintegrants can increase friability, particularly at higher concentrations, since they promote fast disintegration, making tablets more likely to shatter during handling and transportation. The mean hardness of SBFDT- 4 was lower than that of other formed batches because it contained superdisintegrants, which can reduce tablet hardness by promoting rapid disintegration. Higher quantities of superdisintegrants may result in softer tablets.

Fig.3. Assessment parameters of powder



** represents statistical significance of formulation against normal value

Fig.4. Assessment parameters of powder



** represents statistical significance of formulation against normal value

Table No.3.Micromeritic parameters of Sodium Butyrate Formulation development

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	% Compressibility	Hausner's Ratio	Angle of Repose (°)
SBFDT1	0.412±0.06	0.590±0.14	15.168±3.26	1.298±0.10	35.213±2.70
SBFDT2	0.297±0.07	0.542±0.08	20.437±4.35	1.390±0.06	40.477±3.92
SBFDT3	0.620±0.11	0.720±0.16	23.410±2.16	1.230±0.03	37.640±2.61
SBFDT4	0.355±0.04	0.645±0.16	16.717±1.64	1.148±0.04	34.693±2.77
SBFDT5	0.360±0.05	0.668±0.12	24.858±3.90	1.210±0.03	42.173±2.10
SBFDT6	0.375±0.05	0.500±0.17	21.027±1.86	1.160±0.02	44.525±1.8
SBFDT7	0.512±0.05	0.590±0.14	15.168±3.26	1.298±0.10	35.213±2.70
SBFDT8	0.577±0.08	0.542±0.08	20.437±4.35	1.390±0.06	40.477±3.92
SBFDT9	0.598±0.14	0.720±0.16	23.410±2.16	1.230±0.03	37.640±2.61

All values are reported as mean ±SD

Data Optimization:

Quadratic equations

Quadratic equation for the response are as follow:

$$\mathbf{Y = \beta 0 + \beta 1\ A + \beta 2\ B + \beta 3\ AB + \beta 4\ A2 + \beta 5\ B2}$$

Within provided equations, Y symbolizes the independent variable, while 0 denotes the mean response obtained from nine experimental runs, and 1 represents the computed coefficient pertaining to factor A. These equations elucidate the keyproperties of factors A and B, illustrating average response when each factor is independently manipulated across both lower and higher levels.

An analysis of the Design of Experiments (DOE) data strongly indicates that harness, friability, and disintegration time (DT)are significantly affected by the chosen independent parameters. The polynomial equations provided serve as a tool for drawing conclusions based on the mathematical signs within them. A positive sign suggests a synergistic impact, where factors work together, while a negative sign shows an antagonistic outcome, where factors counteract each other.

$Y1 – (Hardness) = 5.25 -0.42\ A -0.72\ B +0.18AB -0.27\ A^2 -0.073\ B^2$

$Y2 – (Friability) = 0.66+ 0.11A + 0.13\ B -0.14\ AB+0.053\ A^2 +0.077B^2$

$Y3 – (DT) = +2.71 -0.12\ A -0.34\ B – 0.12\ AB + 0.048\ A^2 + 0.27\ B^2$

A = Conc. of Cross Povidone

B = Conc. of Cyclodextrin

Statistical analysis

ANOVA was utilized to identify insignificant elements. The findings showed that the p-values for all dependent variables were below 0.05 ($p < 0.05$). Moreover, the model F values for Hardness, Friability and DT were observed to be 10.72,3.34, and 14.13, respectively, signifying their significance (Table no.6-8).

Fig.5. Effect of and Cyclodextrin on Hardness

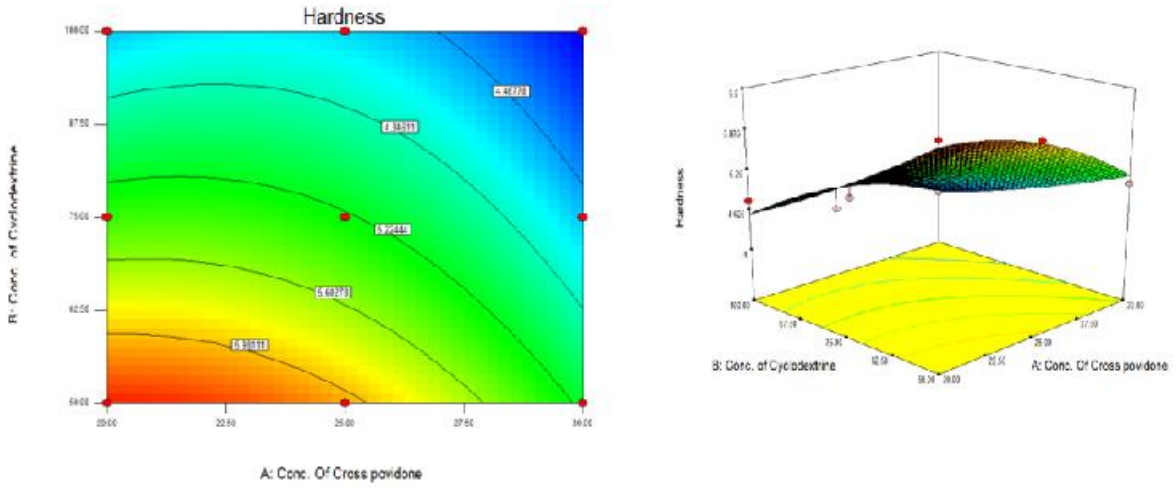


Fig.6. Effect ofCrospovidone and Cyclodextrin on Friability

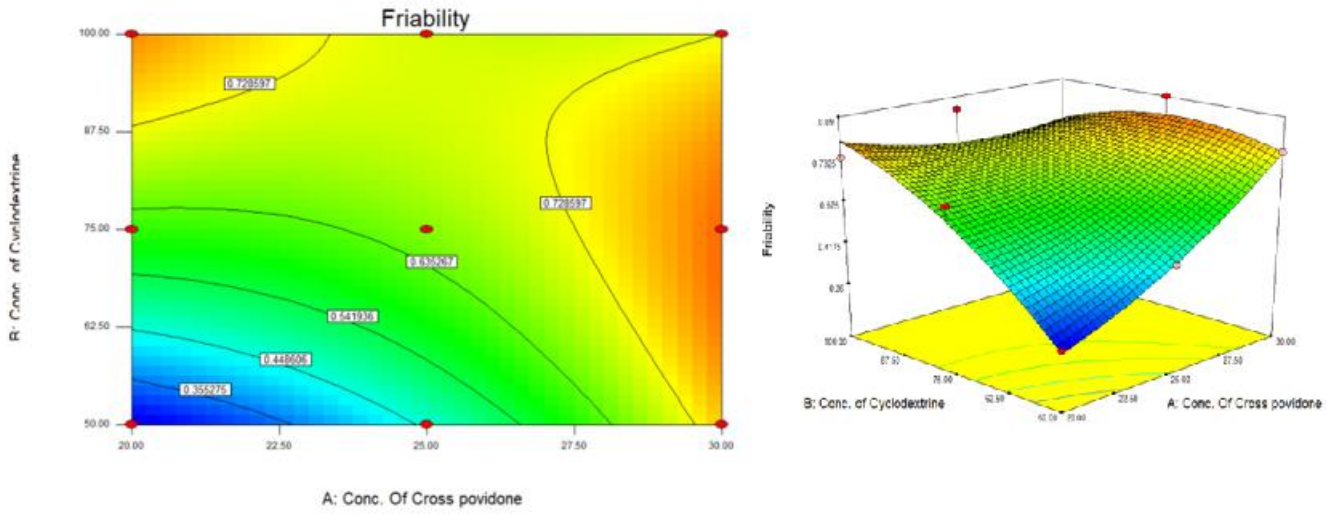


Fig.7. Effect ofCrospovidone and Cyclodextrin on Disintegration Time (DT)

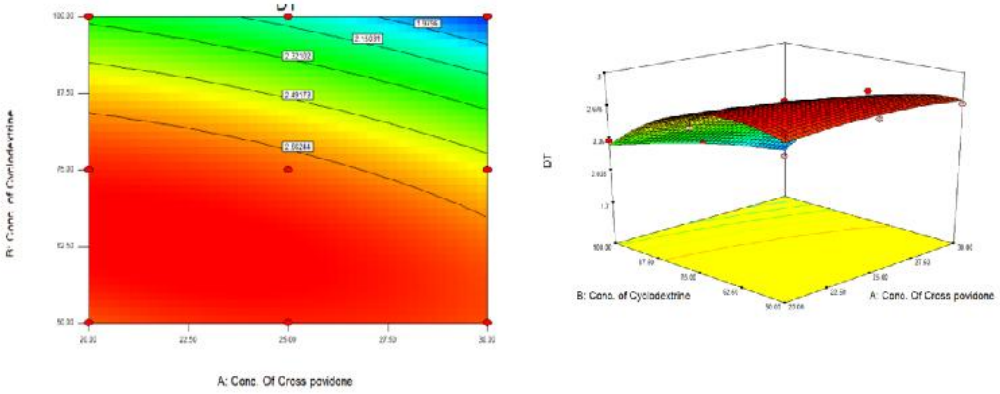


Table No.5.Analysis of variance data for Hardness (Y1).

Source	Sum of square	Df	Mean squares	F-value	p-value	
Model	4.42	5	0.88	10.72	< 0.0001	**Significant**
A-Cross Povidone	1.03	1	1.03	12.52	< 0.0001	
B-Cyclodextrin	3.11	1	3.11	37.68	< 0.0001	
A^2	0.15	1	0.15	1.48		
B^2	0.011	1	0.011	1.79		
AB	0.12	1	0.12	0.13		
Residual	0.25	3	0.083			
Cor Total	4.67	8				

Df- Degree of freedom, F-value -Ratio of two variances and two mean squares, P-value – probabilityfor a given statistical equation.

Table No.6.Analysis of variance data for Friability (Y2)

Source	Sum of square	Df	Mean squares	F-value	p-value	
Model	2.26	5	0.56	8.34	< 0.0001	**Significant**
A-Cross Povidone	1.09	1	1.09	11.34	< 0.0001	
B-Cyclodextrin	3.14	1	4.11	49.12	< 0.0001	
A^2	0.17	1	0.17	1.33		
B^2	0.017	1	0.017	1.79		
AB	0.18	1	0.18	0.34		
Residual	0.047	3	0.016			
Cor Total	0.31	8				

Df- Degree of freedom, F-value -Ratio of two variances and two mean squares, P-value – probabilityfor a given statistical equation.

Table No. 7.Analysis of variance data forDisintegration Time (Y3).

Source	Sum of square	Df	Mean squares	F-value	p-value	
Model	1.00	5	0.20	5.33	< 0.0001	**Significant**
A-Cross Povidone	0.084	1	0.084	14.56	< 0.0001	
B-Cyclodextrin	0.71	1	0.71	49.83	< 0.0001	
A^2	0.017	1	0.55	6.30		
B^2	1.38	1	1.38	15.91		
AB	5.41	1	5.41	62.18		
Residual	0.043	3	0.014			
Cor Total	1.05	8				

Df- Degree of freedom, F-value -Ratio of two variances and two mean squares, P-value – probabilityfor a given statistical equation.

Physical properties of Sodium butyrate FDT

All results of physical characteristicsfor Sodium butyrate FDT were evaluated and are illustrated in Table 4. The weight variance values across all formulations (SBFDT1 to SBDFT9) ranged from 300.12 to 300.1 mg. The friability of the tablet batches between 0.27 to 0.95%.Absolutely, a friability of less than 1% typically falls within the specified limit set by official compendia.Hardness values areobtained in the range of 4.14 – 6.06 $kg/cm^{2.}$.DT of all the tablets was obtained in the range of 1.74-3.98 min.

Table No. 4. Physical properties of Sodium Butyrate tablets

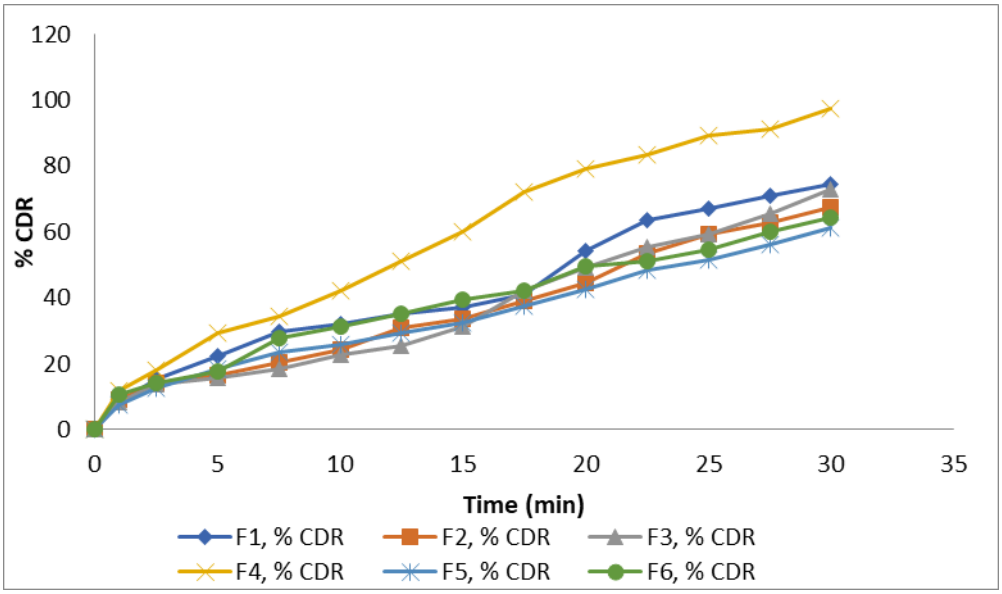
Formulation Code	Factor X1 Conc. of Cross Povidone (Mg)	Factor X2 Conc. of Cyclodextrin (Mg)	Response Y1 Hardness (kg/cm^2)	Response Y2 Friability (%)	Response Y3 Disintegration Time (Min)
SBFDT1	+ (30)	+ (100)	5.60±0.82	0.64±0.15	2.73±0.52
SBFDT2	+ (30)	0 (75)	5.81±0.98	0.72±0.18	2.65±0.49
SBFDT3	+ (30)	- (50)	5.46±0.81	0.45±0.22	2.81±0.70
SBFDT4	0 (25)	+ (100)	4.14±0.59	0.27±0.13	1.74±0.46
SBFDT5	0 (25)	0 (75)	5.29±0.54	0.54±0.12	2.12±0.45
SBFDT6	0 (25)	- (50)	5.04±0.68	0.57±0.18	2.33±0.43
SBFDT7	- (20)	+ (100)	5.80±0.72	0.74±0.20	3.73±0.62

SBFDT8	- (20)	0 (75)	5.91±0.48	0.82±0.45	3.95±0.59
SBFDT9	- (20)	- (50)	6.06±0.71	0.95±0.45	3.98±0.60

Sodium butyrate dissolution study

Batch SBFDT4 had able to produce maximum drug release i.e., 97%, which was provides strong support for using said optimized formulation as compared to remaining batches (Fig.2). The graphical depiction, which clearly shows a higher release rate for SBFDT 4 in contrast to the other formulations, supports this conclusion.

Fig.2. Comparative in vitro drug release study of all batches



Stability Study

All formulations underwent stability tests at room temperature and under accelerated storage conditions, and the physical attributes and drug content of the tablets were examined. The results demonstrated that there had been no physical change to the tablets' appearance based on a visual evaluation. Over 90% of the drug content was present in all formulations while stored at both normal and accelerated temperatures.For each formulation, the degradation rate constants (k) and shelf life (t90) at room temperature show a range of 1.69 to 2.45 day-1 and 413.84 to 901.94 days, respectively.

Conclusion

Sodium butyrate FDT has shown promise in improving the effectiveness of oral administration. After using the combination of crospovidone and cyclodextrin, the resultant tablets show enhanced bioavailability of sodium butyrate and quick disintegration. Patients in need of enhanced gastrointestinal absorption and rapid therapeutic action would benefit most from this development. The study's overall findings emphasize how crucial it is to optimize the formulations of quickly dissolving tablets in order to improve patient compliance and clinical results. To enhance treatment efficacy and patient advantages, future research may concentrate on increasing manufacturing scale and improving tablet characteristics.

FUNDING

None

CONFLICT OF INTEREST

There are no declared conflicts of interest.

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