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Inclusion of novel natural superdisintegrant in fast dissolving tablet formulation using 3^2 factorial design

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ABSTRACT

Fast dissolving tablet (FDT) is commonly used and mostly accepted dosage form due to its various advantages over the other dosage forms. The important component of the FDT is superdisintegrant. There are various natural as well as synthetic superdisintegrant are available and used in formulation. The objective of present work was to find out the alternative for the synthetic superdisintegrant. Which gives cost effective formulation with minimized the drug and excipient interaction. For that the area selected for the study was natural superdisintegrant. In this study the "Ground Nut Shells" i.e. "Peanut Shells" were powdered (GNSP) and investigated for its superdisintegrant property by using the Tramadol Hydrochloride as a model drug. In present study the GNSP was prepared and evaluated for its physicochemical property, phytochemical study, flow property and Particle size analysis. After successful drug and excipient compatibility study with FT-IR and DSC analysis the tablets were prepared by direct compression method by using GNSP in various concentrations 3.33%, 6.66% & 10 % of GNSP by using factorial design. All formulations were evaluated for weight, thickness, hardness, friability, drug content, wetting time, in vitro dispersion, in vitro dissolution study and results obtained were found satisfactory and from that we conclude that the GNSP has significant superdisintegrant potential.

Keywords: Tramadol Hydrochloride, mouth dissolving, Natural Superdisintegrant, Peanut shell, Ground Nut Shell

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INTRODUCTION

Tablet is most widely used dosage form due to its various advantages over the other dosage form such as easy administration and self-medication is possible [1]. Dysphagia is a common problem associated with pediatric as well as geriatric patient [2], many patient have difficulty in swallowing tablet or capsules to overcome this disadvantage the Fast Dissolving Tablet of Mouth Dissolving Tablets are designed [1,3] . US Food and Drug Administration center for drug and Evaluation and research (CDER) defines in orange book FDT as "a solid dosage form containing medicinal substances, which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue. And European Pharmacopoeia adopted word "Orodispersible tablet" and described as 'Uncoated tablet intended to be placed in the mouth where they disperse rapidly before being swallowed and tablet should disintegrate within 3 min. [4]. FDT are the formulations which dissolve in few seconds and release the active ingredient at faster rate [5]. FDT are single unit dosage form, when placed in mouth allows to disperse or dissolve in saliva without need of water and provide quick onset of action [6].

Tramadol HCl is centrally acting opioid analgesic and structurally related to the morphine and codeine which are used in treatment of moderate to severe painin disease conditions [7]. Tramadol HCl that's why selected as the model drug. In pain condition patient require faster relief for that the Tramadol is given by the intravenous route but this is the painful process so the tablet dosage form was selected. FDT formulation was selected for the study and as tramadol have bitter taste the sweeter such as Sodium Saccharine is used in the formulation. The superdisintegrant is the heart of the FDT;today in market various natural as well as synthetic superdisintegrants are available. The natural superdisintegrant has several advantages over the synthetic one such as cost effective, low possibility of interaction with the API so by keeping this point in mind the proposed work was carried out in order to investigate the superdisintegrant properties of the Ground Nut (Pea Nut) Shells powder.

MATERIALS AND METHODS

Material-
Tramadol Hydrochloride was obtained as gift sample form the Glenmark Research and Development Center, Sinnar, MH, India, the Ground Nut was obtained from the local farmer Mr. Kolpe, form the Kolpewadi, MH, India. The other necessary chemicals such as Avicel, Magnesium stearate were purchased form Research lab Finechem Mumbai while Talc, Sodium saccharine and lactose etc. were purchased from the Loba Chem.

Methods-
A.)Preparation of GNSP- Ground Nuts werewashed with the water to remove the soil then sundried for 1 day. After that Shells were separated and placed in hot air oven for 30 minute at 100 ^{0}C then shells were crushed in grinder and then passed though # 60 mesh.

Characterization of GNSP-
a.) Phytochemical Study-
For the Characterization of GNSP the various phytochemical tests and flow property study of only GNSP was carried out [8].

b.) Particle Size Determination-
The particle size of the GNSP was determined by the Mastersizer (Malvern). The suspension of 0.5 gm. of GNSP was prepared by using drop Tween 80 as suspending agent then analyzed in the Mastersizer.

B.) Calibration Curve of Tramadol HCl in 6.8 pH phosphate buffer-
20 mg of Tramadol HCl was weighed and dissolved in sufficient amount of phosphate buffer of 6.8pH and volume was made up to 100 ml with the same solution. By using the above stock solution with appropriate dilutions the 20,40,60 up to 200 µg/ml dilutions were prepared and absorbance of these solutions were estimated using UV spectrophotometer (Shimadzu 1660 PC) at 271 nm [9].

C.)Solubility Study of Tramadol HCl-
Solubility of the Tramadol HCL was determined in different media (distilled water, 0.1 N HCl, phosphate buffer pH 6.8). Excess amount of drug was transferred in volumetric flasks containing different solvents and was shaken until saturation was achieved; the flask was sonicated for 30 min. then after filtration 1 ml of above solution was diluted up to 10 ml with respective solvent and absorbance was measured at 271 nm using UV spectrophotometer [9].

D.)Drug and Excipient Compatibility Study
a.) Fourier Transform Infrared Spectroscopic (FTIR) Analysis-
The FTIR spectrum of Tramadol HCl and GNSP blend was studied by using FTIR spectrophotometer (Shimadzu 8400 S) using eudragit film. The Scanning range was 500-4000 cm^{-1} and the resolution was 1 cm^{-1}, this spectral analysis was employed to check the compatibility of drug with the excipient used.

b.) Differential Scanning Calorimetry (DSC) Analysis-
The DSC study was carried out by using DSC-60 instrument (M/s Shimadzu) to check the compatibility of Tramadol HCL and GNSP DSC thermogram of Tramadol HCl and GNSP were individually taken for their identical endothermic reaction. Finally physical mixture of all above ingredient was scanned for DSC.

E.) Pre-compression Study-

a.) Bulk Density-

Bulk Density of tablet blend was measured by pouring the 10 gm. of blend in measuring cylinder then after volume was measured and bulk density was calculated using following formula [9],

$$\textbf{Bulk Density} = \frac{\boldsymbol{Mass\ of\ Powder}}{\textbf{Volume of Powder}}$$

b.) Tap Density-

The Tap Density of tablet blend was measured by pouring the 10 gm. of blend in measuring cylinder then allowed for 100 taps in the Tap density test apparatus then the volume was measured and tap density was calculated by using following formula [9],

$$\textbf{Tap Density} = \frac{\boldsymbol{Mass\ of\ Powder}}{\textbf{Volume of Powder after 100 taps}}$$

c.) Hausner's Ratio-

Hausner's ratio is the ease of index of powder flow and calculated by using following formula [10],

$$\textbf{Tap Density} = \frac{\boldsymbol{Tap\ Density}}{\boldsymbol{Bulk\ Density}}$$

d.) Carr's Index-

Percent compressibility of blend was determined by Carr's compressibility index, calculated by using following formula [9],

$$\textbf{Carr's Index} = \frac{\boldsymbol{Tap\ Density - Bulk\ Density}}{\boldsymbol{Tap\ Density}}\ \boldsymbol{X}\ \textbf{100}$$

e.) Angle of Repose-

Angle of repose was determined using funnel method. The blend was poured through a funnel on the graph paper to form a pile and then pile height (h) was measured. The radius of the heap (r) was measured and angle of repose was calculated by using following formula [10].

$$\textbf{Angle of Repose } (\theta) = (\boldsymbol{tan})^{\boldsymbol{-1}} \frac{\boldsymbol{Height\ of\ Pile\ (h)}}{\boldsymbol{Radius\ of\ Heap\ (r)}}$$

F.) Preparation and Evaluation of Fast Dissolving Tablet-

For the preparation of the FDT the varying concentration of GNSP and Avicel pH 101 were used the final volume 150 mg was adjusted by using lactose.

All ingredients individually passed through sieve number # 60 mesh, after accurate weighing the all ingredients were mixed then blend was taken in polybag and shaken for 15 min for uniform mixing. Then tablet of 150 mg prepared by using the 8 mm round punch (Cambridge 9 Station Rotatory Tablet Punching Machine).

Table No. 1- Composition of Various Batches (Quantity in mg/tablet)

Batch	Tramadol	GNSP	Avicel pH101	Lactose	Sodium Saccharine	Magnesium Stearate	Talc
Plain1	50	0	45	40	6	4	5
Plain2	50	10	0	75	6	4	5
A	50	5	30	50	6	4	5
B	50	5	35	45	6	4	5
C	50	5	40	40	6	4	5
D	50	10	30	45	6	4	5
E	50	10	35	40	6	4	5
F	50	10	40	35	6	4	5
G	50	15	30	40	6	4	5
H	50	15	35	35	6	4	5
I	50	15	40	30	6	4	5

Evaluation of Fast Dissolving Tablet-

a.) Thickness-

Thickness of 3 tablets was measured by using vernier caliper.

b.) Hardness-
Hardness /Crushing Strength (diametric crushing force) is a force required to break the tablet across the diameter. The hardness of the tablet is indication of its tensile strength and Hardness of 3 tablets was measured by using the Monsanto hardness tester.

c.) Friability-
Friability 17was determined taking tablets equivalent to a weight of approximately 6.5 g. Tablets samples were weighed accurately and placed in friabilator (Electrolab friabilator). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear. The intact tablets were reweighed. And friability was calculated using the following formula,[9,10]

$$\% \textbf{ Friability} = \frac{\boldsymbol{Initial\ Weight - Final\ Weight}}{\boldsymbol{Initial\ Weight}} \boldsymbol{X\ 100}$$

d.) Weight Variation-
20 tablets of each of formulation were weighed individually and together using an electronic balance. The average weight was calculated and individual tablet weight was compared with average value and the deviation was recorded. According to the Specification ± 7.5 % Deviation in the tablet weight is acceptable.[9]

e.) Drug Content Uniformity-
Ten tablets from each batch were powdered. Then powdered sample equivalent to 20 mg of drug was transferred to a volumetric flask and volume make up to 100 ml using phosphate buffer of pH 6.8, from that by accurate dilutions the concentration of 100 µg/ml was prepared and compared with the 100µg/ml solution of pure drug and it was determined by UV spectroscopy at 271 nm.[9,10]

f.) Wetting Time-
A piece of tissue paper folded twice was kept in a Petri dish (inter diameter 5.5cm) containing 6ml of purified water. The tablet was placed on that tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was recorded. [11]

g.) In Vitro Dispersion Study-
The disintegration time for mouth dissolving tablets needs to be modified, as disintegration is required without presence water; thus the test should carried out in content similar to salivary content. For this purpose, a Petri plate was filled with 9 ml of phosphate buffer solution, pH 6.8 (which correlated pH of saliva). The tablet was carefully put in it and time for the tablet to completely disintegrate into fine particles was noted in seconds [9].

h.) In Vitro Disintegration Study-
The disintegration time of the tablet was measured by using water as solvent (37±2°C) according to USP disintegration test with disk. Three tablets from every batch (formulation) were tested for the disintegration time. The *in-vitro* disintegration time was determined in seconds using Electrolab Disintegration Test Apparatus [9].

i.) In Vitro Dissolution Study-
The *in-vitro* dissolution study was carried out using 6.8 pH phosphate buffer as dissolution medium with 50 rpm speed using USP Type-II (Paddle) dissolution apparatus. The study was carried out in 900 ml of 6.8 pH phosphate buffer for 30 min maintained at 37 ± 0.5°C. At the every time point 5 ml of sample is withdrawn replenish with equal volume of 6.8 pH phosphate buffer. Time points 1, 2, 3, 5, 10, 15, 30, 45,60 min [9].

G.) Response surface and Counter Plots-
The mathematical equations for the effect of the two variables GNSP and Avicel on the Hardness, Disintegration and Dispersion time was derived by using PCP Disso V3i software. By using same the Response surface and Counter plots were obtained.

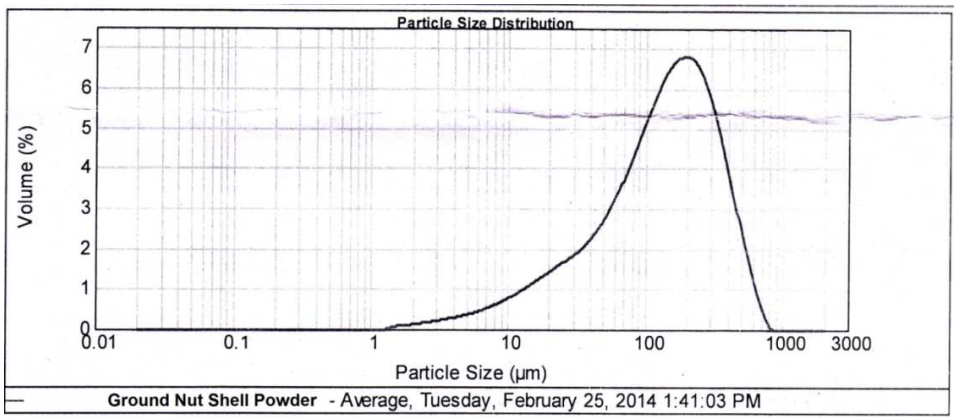
H.) Stability Study-
The stability study of the optimized formulation was studied The optimized formulation was placed up to 3 months in both condition of 25°C/60 % RH and 40°C/75% RH. And at every month the following parameters were studied.

RESULTS AND DISCUSSION

A.)Characterization of GNSP-
Synonym- Peanut, Ground Nut, Mongphali
Family-Fabaceae
Sub Family- Faboideae
Genus- Arachis
Species- Arachis Hypogea

a.) Phytochemical Investigation-
The chemical composition of Ground Nut Shell (peanut shells) is 8.2% protein, 28.8% lignin, 37.0% cellulose and 2.5% carbohydrate.

b.) Particle Size Determination-
The particle size study was done by using Malvern Instrument Mastersizer and result obtained was as follows, The d(0.10) =22.403 µm , d (0.50) =139.001 µm , and d (0.90) = 371.182 µm , that means the 90% particles have the size below 371.182 µm.



FigureNo.1 - Particle Size Distribution of GNSP

B.) Calibration Curve of Tramadol Hydrochloride in 6.8 pH phosphate buffer-
For this absorbance value obtained are listed as below and it shows regression 0.9764 and values found were linear.

Table No.2- Calibration Curve for Tramadol HCl in 6.8 pH phosphate buffer

Sr. No.	Conc. (µg/ml)	λ max (271)
1	0	0
2	20	0.082
3	40	0.125
4	60	0.272
5	80	0.458
6	100	0.63
7	120	0.753
8	140	0.951
9	160	1.06
10	180	1.226
11	200	1.147

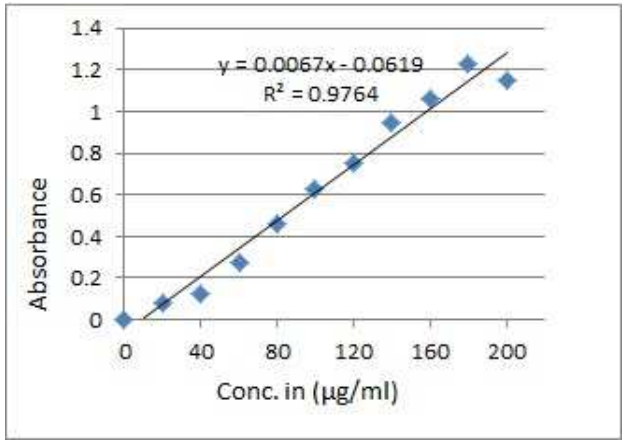


Figure No.2- Calibration curve and for Tramadol HCl

C.)Solubility study of Tramadol Hydrochloride-

The solubility study Solubility of the Tramadol HCL was determined in different three media distilled water, 0.1 N HCl, pH 6.8 phosphate buffer and results as below,

Table No.3- Solubility Study of Tramadol in various solvents

Sr. No.	Media	Solubility (mg/ml)
1.	Distilled Water	1.761
2.	0.1 N HCl	1.725
3.	6.8 pH Phosphate Buffer	1.893

D.)Drug and Excipient Compatibility Study-

a.) Fourier Transform Infrared Spectroscopic (FTIR) Analysis-

FT-IR spectra for Tramadol HCl, GNSP as well as their physical mixture were obtained and various functional groups were detected. Characteristic stretching is shown in Table No.4- IR spectrum of Tramadol hydrochloride is shown in Fig.No.-3. The major peaks observed in IR Spectra of Tramadol Hydrochloride are given as Pure Drug and the IR Spectra of Physical mixture Tramadol Hydrochloride with the GNSP is given as mixture and both were compared and no major interaction was noted in the ranges of IR Spectra so both Drug and Excipient so we conclude that the Tramadol HCl and GNSP were found to be compatible and suitable for formulation.

Table No.4–Infrared Spectroscopy study Peaks of Drug and Excipients

Functional Group	Principle Peaks Observed at		Inference
	Pure Drug	Mixture	
C-O Strech	1251	1261	No Major Interactions were observed in the IR Spectra of Tramadol Hydrochloride and its physical mixture with GNSP Powder
C-N Strech	1350	1350	
CH_3Bend	1365	1370	
C=C Strech	1633	1647	
C-H Strech Aliphatic	2655	2660	
C-H Strech Aromatic	2950	2952	
O-H Strech	3350	3350	

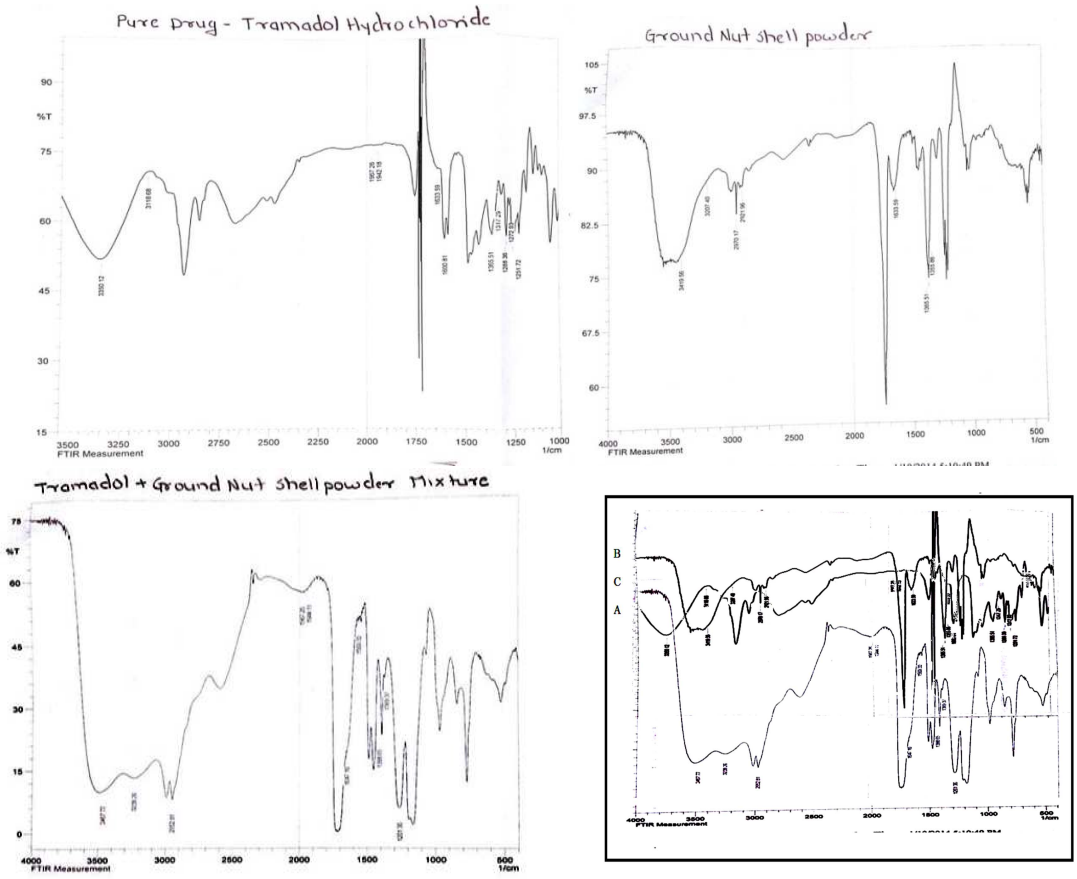


Figure No.3- FT-IR of:a) Tramadol HCl, b) GNSPc.) Tramadol+ GNSP

d.) Overly spectra of a, b and c

c.) Differential Scanning Calorimetry (DSC) Analysis-

The DSC curves obtained for pure Tramadol HCl, GNSP and their mixture. Pure Tramadol HCl showed a melting endotherm at 182^{0}C and the physical mixture of drug andexcipients showed the melting endotherm at 182°C that means the drug melting point is not changed. Presence of all peaks indicates that all ingredients are compatible with each other.

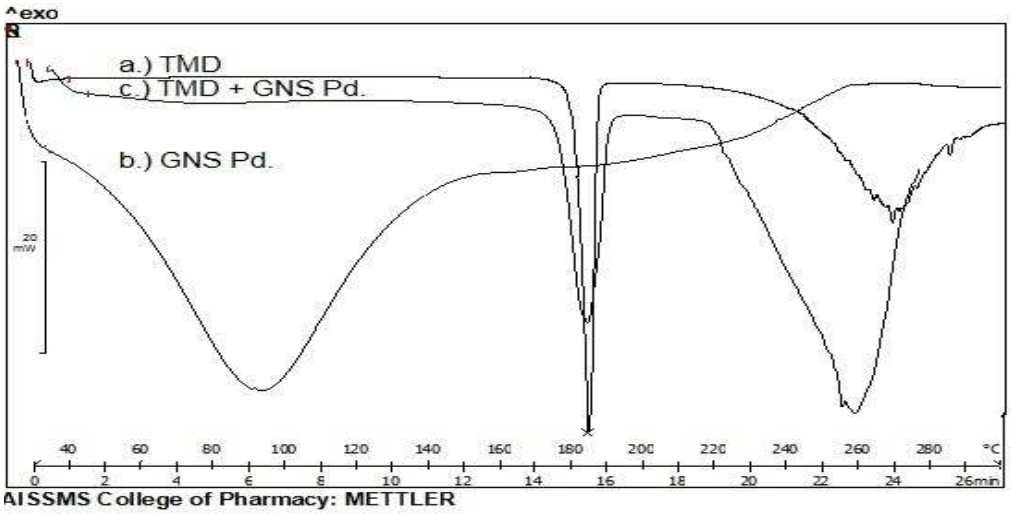


Figure No.4-DSC thermogram of: a) Tramadol, b) GNSP c.)Mixture

E.) Pre-compression Study-

The pre-compression parameters of all batches were studied, all the batches shows the good flow properties and the obtained results were as tabulated below-

All the batches show the Angle of Repose in between the 32-35, which shows the passable flow property.

Batch A to F shows the Carr's index between 18 to 19 which shows the fair passable compressibility property while the G to I shows the more than 22 which shows the poor compressibility property so the batches A to F shows the good compressibility index.

Table No.5- Pre-compression Study-

Batch	Bulk Density (gm/ml)	Tap Density (gm/ml)	Carr's Index	Hausner's Ratio	Angle of Repose (Ɵ)
Plain1	0.61	0.68	10.14	1.10	32.62
Plain2	0.50	0.67	34.90	1.35	32.82
A	0.58	0.69	18.75	1.21	35.37
B	0.58	0.69	18.62	1.21	33.82
C	0.57	0.68	19.18	1.21	32.62
D	0.52	0.62	18.52	1.23	34.21
E	0.52	0.61	17.58	1.23	33.82
F	0.51	0.61	19.63	1.23	33.02
G	0.49	0.60	22.89	1.23	34.61
H	0.49	0.60	22.02	1.22	34.21
I	0.48	0.59	22.49	1.22	32.62

F.) Evaluation of Fast Dissolving Tablet-

The prepared tablet were evaluated for various parameters, thickness, diameter, weight variation etc. evaluation were found within the limit and other parameters such as hardness, disintegration, dispersion, wetting time, water absorption ratio and content uniformity etc. were varies with the conc. of GNSP And Avicel and the obtained results of physicochemical evaluation of tablets are given in Table 6.

As the material was free flowing, tablets were obtained of uniform weight due to uniform die filling. Hardness of tablets was between 2.9-3.4 kg/cm^2(except Plain 1) for all the formulations.

The thickness of all batches was found constant.

Friability was found in between 0.00-0.97%. The friability value below 1% was an indication of good mechanical resistance of the tablet.

All A to I formulation shows the shorter disintegration and dispersion time which is helpful for the improving the bioavailability of the formulation. The minimum time for the dispersion is less than 3 minutes while all the formulations shows theshorter dispersion time which is beneficial than other formulation.

The wetting time for batch A to C was found to be 19-22 seconds, while for batch D to F it was 15-18 seconds and for the last 3 batches G to I it was 9 to 10. This indicates the formulation requires minimum time to get wet the tablet and which is helpful for the faster disintegration.

The drug content of the formulation was measured by the UV spectrophotometry by preparing the standard solution of pure drug and sample solution prepared by taking the drug equivalent to the standard form the tablet powder. The absorbance was measured for various concentrations and the % drug content was found to be 95-99% which was within the acceptable limits.

Table No.6- Evaluation parameters results

Batch	Hardness (kg/cm^2)	Disintegration (Sec.)	Dispersion (Sec.)	Wetting time (Sec.)	Content Uniformity (%)
Plain1	4	65	90	35	96.98
Plain2	2.9	25	35	18	95.56
A	3.2	16	24	22	98.89
B	3.2	14	22	20	98.41
C	3.3	14	21	19	98.10
D	3.1	12	17	18	98.25
E	3.2	10	15	16	98.89
F	3.2	9	14	15	99.21
G	3	8	11	12	97.78
H	3.1	7	9	10	99.21
I	3.1	6	8	9	99.37

Dissolution Study-

The Dissolution study for the all batches was carried out in 6.8 pH phosphate buffer for the 30 min. the Plain I and Plain II batches shows the release 59% and 73 % drug release respectively, batch A to C shows 86-87 %, D to E shows 91 to 92 % while F to G shows the 94 to 96 % drug release which is maximum. The following results were obtained in the dissolution study.

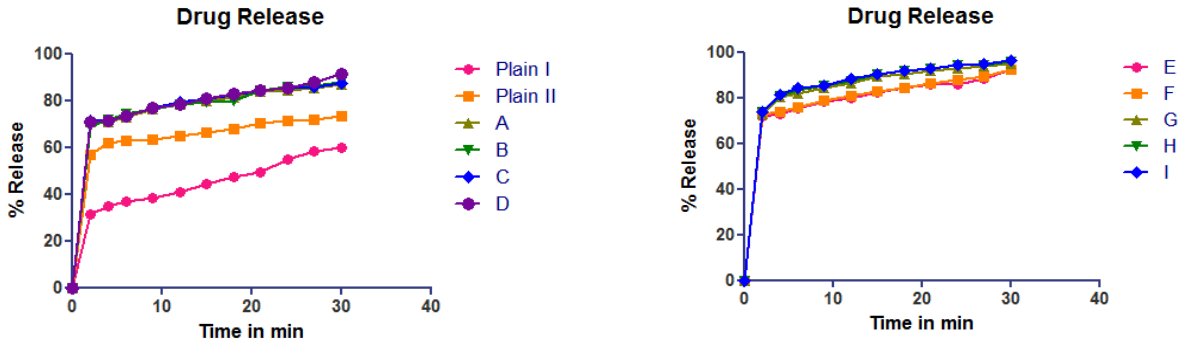


Figure No. 5-Dissolution Profile of all 11 batches of A.) Plain I to D; and B.) E to I

G.) Response surface Graph and Counter Plot-

The effect of the 2 variables X_1 and X_2 on the Hardness, Disintegration time and dispersion time was studied by using the factorial design, and the Response surface and counter plots were obtained as below,

a.) For Hardness-

The mathematically generated equation for the Hardness was found to be significant with the F-value =17.57 ($p<0.05$) and **R= 0.8541**

Mathematically Generated Equation,

$$\mathbf{Y_1 = 3.1667 - 0.0833\ X_1 - 0.0667\ X_2 \quad \text{(eq.1)}}$$

The above equation clearly explains the relationship between the GNSP and the Avicel with the Hardness.

The negative sign indicates that the GNSPand Avicel also shows the negative effect on the hardnes that means as the amount of the GNSPand Avicel increases the Hardness decreases slightly. Ground nut affects on hardness 1.30 folds more than that of Avicel.

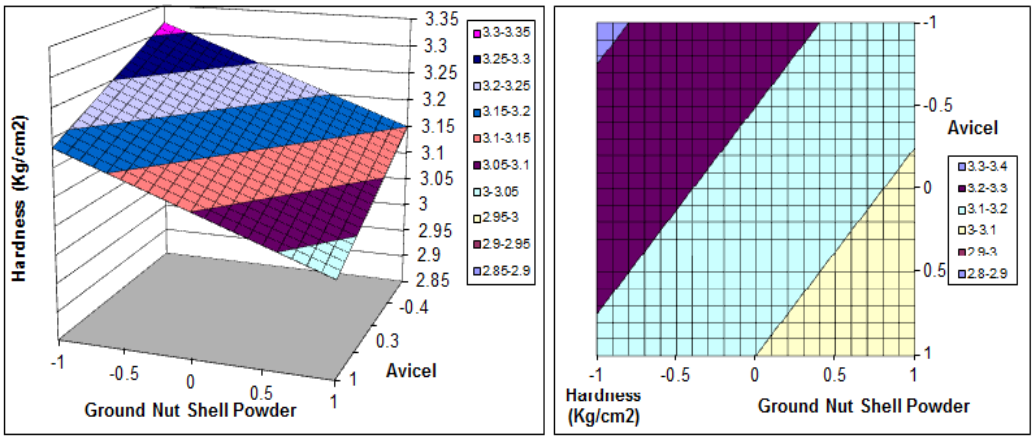


Figure No.6- Response surface and counter plot for Hardness

b.) For disintegration time-

The mathematically generated equation for the Disintegration Time was found to be significant with the F-value =173.4 ($p<0.05$) and **R= 0.9829**

Mathematically Generated Equation,

$$Y_2 = 10.667 - 3.8333\ X_1 - 1.1667\ X_2 \text{\_\_\_\_\_(eq.2)}$$

The above equation clearly explains the relationship between the GNSP and the Avicel with the Disintegration time. The negative sign indicates that the GNSP and Avicel shows the negative effect on the disintegration time that means as the amount of the GNSPand Avicel increases the disintegration time falls down and tablet disintegrates more quickly. The above equation clearly shows that the GNSPaffects on disintegration time 3.30 fold more than that of Avicel.

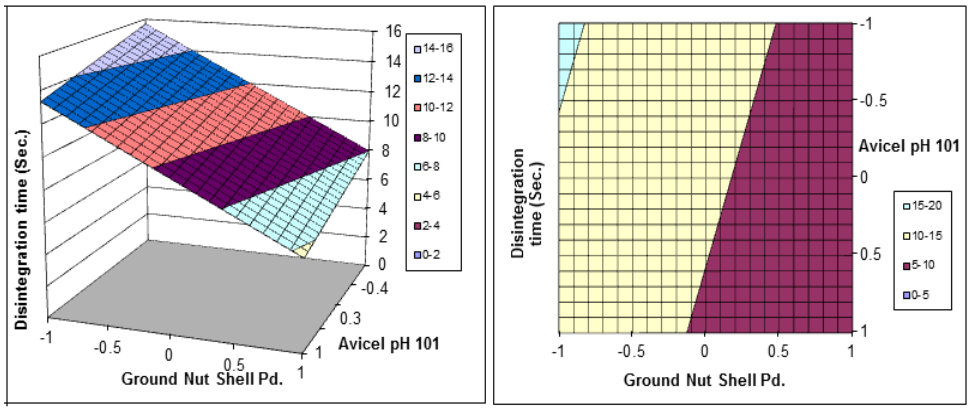


Figure No.7- Response surface and counter plot for Disintegration Time

c.) For Dispersion time-

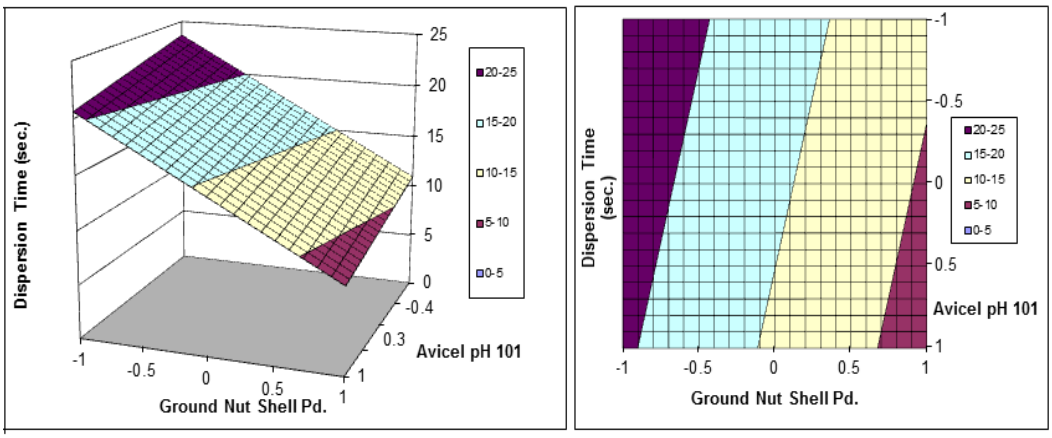
The mathematically generated equation for the Disintegration Time was found to be significant with the F-value =173.4 ($p<0.05$) and **R= 0.9972**

Mathematically Generated Equation,

$$Y_3 = 15.7778 - 6.33\ X_1 - 1.5\ X_2 \text{\_\_\_\_\_(eq.3)}$$

The above equation clearly explains the relationship between the GNSP and the Avicel with the Dispersion time.

The negative sign indicates that the GNSP and Avicel both shows the negative effect on the dispersion time that means as the amount of the GNSP and Avicel increases the Dispersion time falls down and tablet get dispersed fast. The above equation clearly indicates that the GNSPaffects on the Disintegration time 4.22 fold more than that of Avicel.



FigureNo.8- Response surface and counter plot for Dispersion Time

H.) Stability Study-

The optimized formulations were placed up to 3 months in both condition of 25°C/60 % RH and 40°C/75% RH. And at every month the necessary parameters were studied. And results found were within the range. No major changes were observed in the evaluation parameters such as Hardness, Friability, Dissolution, Disintegration and Dispersion time. So the formulation passed stability study successfully.

Summary-

In the present research work the GNSP was very first time used as superdisintegrating agent in 3.33, 6.99 and 10 %. After the successful drug and excipient compatibility study by using the FT-IR spectroscopy and DSC the powder blend was prepared and evaluated for pre-compression parameters then after the tablet were punched using Rotary Tablet punching machine with 8 mm punch. The formulated tablets were evaluated for the various evaluation parameters. While evaluating them we observed the effect of the GNSP on the Hardness, Friability, Dissolution and Disintegration Time.

As the percentage of the GNS powder increased the hardness decreases slightly, and the dispersion gets quicker as compare to tablet containing lower percentage of the GNSP. In present study we formulated 11 different batches one by using GNSP only and another by Avicel only remaining 9 batches formulated by varying concentration of the GNSP and MCC with 3^2 Factorial design formulated and to investigate its effect on various parameters.

During the study we observed that, the Batch A, B and C has more hardness and less friability as compared to the other batches and Batch G, H and I shows the more faster drug release as compare to other batches. And the batch D, E and F shows the optimum hardness with better dissolution and better dispersion time.

Batch A, B and C shows the drug release about more than 80% within 15 minutes about 60 % drug release achieved in 30 minutes. In case of batch D, E, and F the time required to release more than 80% drug was less than 12 minute and at the 30^{th} minute it shows 92 to 94 % drug release. And in case of batch G, H and I after 4^{th} minute the 80 % of drug released was achieved and 94 to 95 % drug release was observed at 30^{th} minute.

CONCLUSION

The present investigation revealed high superdisintegration potential of GNSP. The FDT of Tramadol HCl was prepared by using the Factorial Design and the various 9 batches weredesigned. All 9 batches showed the satisfactory results, but amongst them batch D, E and F was found to be best formulation as it shows the optimum

hardness as well as optimum dissolution and disintegration time. So we can able to use the GNSP as superdisintegrant and formulate the FDT in low cost and by avoiding the synthetic superdisintegrants.

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