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DESIGN AND DEVELOPMENT OF DANTROLENE SPHERICAL AGGLOMERATES FOR IMPROVEMENT IN BIOAVAILABILITY

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Keywords:

Spherical agglomeration, Dantrolene, Bioavailability, Dissolution, Flowability

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ABSTRACT: The purpose of this research was to obtain directly compressible agglomerates of Dantrolene using spherical agglomerates. Spherical agglomeration technique enables simultaneous crystallization and agglomeration. Sodium hydroxide acted as a good solvent, aqueous solution of PEG 6000 in hydrochloric acid served as bad solvent and isopropyl acetate was used as bridging liquid. The optimization of formula was carried out by using 2^3 factorial design, where the factors were speed of rotation, polymer: drug ratio and amount of bridging liquid. The responses evaluated were % drug release, MYP and Carr's Index. The optimized agglomerates and Dantrolene was evaluated by powder X-ray diffractometry (PXRD) and scanning electron microscopy (SEM). PXRD showed reduction in crystalline nature of Dantrolene and SEM demonstrated spherical and smooth surface. The agglomeration improved the micromeritic properties of Dantrolene (Carr's index16 and hausner ratio between 1.2 and mean yield pressure 3.58 tons). *In-vitro* dissolution increased by 10 fold. The AUC (35.19%), C_{max} (23%) and t_{max} (reduced by 1 h) also recorded improvement. From the results, the conclusion is that spherical agglomerates is a suitable alternative method to the granulation process and can be used for design of immediate release formulation.

INTRODUCTION: Dantrolene, a hydantoin derivative, classified as direct-acting skeletal muscle relaxant depresses excitation-contraction coupling in skeletal muscle [1]. Particle engineering techniques enable formulator to improve dissolution as well as flow and compression characteristics of active pharmaceutical ingredients such as Dantrolene. This not only make it amenable to large scale manufacture of solid dosage forms but also improves therapeutic efficacy by improving dissolution.

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Spherical crystallization is one the particle engineering techniques where a near saturated solution of the drug in good solvent is poured into a poor solvent. Due to higher affinity between good and poor solvents the drug undergoes precipitation. The precipitated crystals are kept in stirring with addition of a wetting liquid (bridging liquid) which due to interfacial tension effects and capillary forces, causes crystals to agglomerate resulting in the formation of larger size agglomerates [2-4].

The present work describes formation of agglomerates of dantrolene to enhance flow, compression and dissolution properties, a 2^3 factorial design was employed where stirring speed, polymer: drug ratio and volume of bridging liquid were optimized to achieve the agglomerates that will have required flow, compression and drug release properties.

MATERIALS AND METHODS:

Materials: Dantrolene was gift sample from Sankalp Healthcare and Allied Products Pvt. Ltd. polyethylene glycol 6000 was supplied by Loba chemicals, Mumbai.

Method:

Analytical Method: UV calibration curve: Standard solutions of dantrolene in distilled water of concentrations 5-25 µg/ml were prepared from (1 µg/ml) methanolic solution of dantrolene. The absorbance of all the solutions was measured using distilled water as blank at 395 nm using double beam UV spectrophotometer. A standard plot of absorbance v/s concentration of drug in µg/ml was prepared. Correlation co-efficient and regression equation were obtained from calibration curve.

Spherical Agglomeration: [5] Dantrolene sodium was crystallized using 1M NaOH, 0.1M HCl, isopropylacetate system Dantrolene (6 g) and was dissolved in 20 ml of 1 M NaOH and agglomerated in solution of hydrophilic polymer PEG 6000 (3 g polymer in 30 ml 0.7 M HCl) under agitation. Isopropyl acetate was added as bridging liquid. The temperature of the crystallization system was maintained at 5 °C and stirring for about 15 min the agglomerates obtained were filtered and dried over-night. A 2^3 factorial Design containing 8 experimental runs to evaluate three variables *viz*. polymer: drug stirring speed and amount of bridging liquid at 2 levels was employed to determine their effect on three responses *i.e.* MYP, dissolution, Carr index and their interaction there in. The layout of the experimental design is shown in **Table 1**.

TABLE 1: LAYOUT OF THE EXPERIMENTAL DESIGN

Formulation code	Stirring speed (rpm)	Polymer: drug ratio (g)	Amount of bridging liquid (ml)
1	400	0.5:1	2
2	400	1.5:1	2
3	700	0.5:1	2
4	700	1.5:1	2
5	400	0.5:1	1
6	400	1.5:1	1
7	700	0.5:1	1
8	700	1.5:1	1

Evaluation of Crystallo Co Agglomerates:

Drug Content: Drug content was determined by dissolving samples of agglomerates (10 mg) in 10 ml of acetonitrile. The solution was filtered through Whatman filter paper no. 41, suitably diluted and the absorbance was measured at 395 nm.

Micromeritic Studies: [6, 7] Angle of repose was determined by fixed funnel method whereas Carr's Index and Hausner ratio were calculated from bulk density and tapped density using methods described in literature.

Heckel Analysis: [8] The Heckel analysis was performed on bulk drugs and agglomerates using discs prepared at compaction pressure of 2, 4, 6, 8, 10, 12 tonnes in KBr press (technosearch instruments, Model-M-15) using 13.00 mm flat faces punches, the diameter, height, and weight of the tablets was measured and Heckel analysis was performed by plotting log relative density *vs*. pressure.

Dissolution Studies: [9, 10] The dissolution rate studies were conducted in 900 ml of 0.5% methylbenzethonium chloride in water pH 6.8 at 100 rpm maintained at 37 ± 0.5 °C in a basket type dissolution apparatus (Model TDT-08L, Electrolab). 80 mg of drug and agglomerates of PVP, HPMC and PEG 6000 equivalent to 80 mg of drug were added to dissolution medium and the samples were withdrawn at appropriate time intervals. The samples were immediately filtered through 0.45 µm membrane filter, suitably diluted and analyzed spectrophotometrically at 395 nm. The data obtained from dissolution studies were statistically validated.

Saturation Solubility Studies: [11] Dantrolene sodium selected in the present work has poor aqueous solubility characteristics. To determine the aqueous solubility of Dantrolene sodium, saturation solubility study has been carried out. Saturation solubility studies were performed in phosphate buffer pH 7.4 in triplicate according to the method reported by Higuchi and Connors. Excess of Dantrolene sodium (50 mg) and agglomerates of PVP, HPMC and PEG 6000 equivalent to 50 mg of drug were added to 20 mL of phosphate buffer pH 7.4 taken in screw cap tube and shaken for 24 h in rotary flask shaker at 37 ± 0.5 °C to achieve the equilibrium. Appropriate aliquots were then withdrawn and filtered through Whatman filter paper no. 41 and analyzed spectrophotometrically at 395 nm. The results obtained from saturation solubility studies were statistically validated.

Scanning Electron Microscopy (SEM): [12, 13] The surface morphological properties of Crystallo-co-agglomerates of for optimized batch PEG 6000 and pure drug was investigated by scanning electron microscopy (SEM-Jeol Instruments, JSM-6360, and Japan). Samples were mounted on a double-faced adhesive tape, sputtered with gold. Scanning electron photographs were taken at an accelerating voltage of 20 kV and obtained micrographs were examined at ×100, magnification.

Powder X-ray Diffractometry (PXRD): [14, 15] X-RD is an important tool to determine the formation and changes occurs in the nature of crystals of Dantrolene sodium with diluents. Also, it indicates the % crystallinity of Crystallo-co-agglomerates. The X-RD data of Crystallo-co-agglomerates of optimized batch of PEG 6000 and pure drug were recorded on a Bruker XRD (Model: D 8 Advance) with copper target. The conditions were: 40 kV voltages; 40 mA current; at room temperature. The samples were loaded on to the diffractometer and scanned over a range of 2θ values form 10 to 80º at a scan rate of 0.05 º/min.

Preparation and Evaluation of Dantrolene Tablet using Agglomerates: The optimized agglomerates were subjected to direct compression after addition of different excipients. Evaluation of tablet such as thickness and diameter, hardness, friability, weight variation, disintegration time and dissolution was carried out by using methods reported in literature.

All the materials are shown in **Table 2**. The material was then mixed by geometric mixing technique. Mixing was continued for about 30 minutes until a homogenous powder blend was obtained. Lactose was used as diluent, PVP K-30 was used as dry binder, SLS was used as dispersing agent, talc was used as lubricant and starch as disintegrant.

TABLE 2: FORMULA FOR PREPARATION OF TABLETS

S. no.	Ingredient	Amount (mg)
1	Dantrolene sodium crytalllo co agglomerates	80
2	Starch	4.5
3	SLS	3
4	PVP K-30	12
5	Talc	3
6	Lactose	QS

#Total weight of the tablets was kept 150 mg

Tablets were prepared by direct compression method using standard 10.5 mm concave punches on rotary tablet compression machine (Rimek Mini Press II MT).

***In-vivo* Pharmacokinetic Analysis:**

Preparation of Standard Stock Solutions: Standard stock solution of Dantrolene Sodium and Nitrofurazone (1 mg/ml) were diluted with methanol to get series of working standard solutions having concentration 1, 5, 10, 20, 40, 60, 80 and 100 µg/mL. 0.2 mL of Nitrofurazone stock solution was further diluted to 10 mL with methanol to get standard solution of concentration 20 µg/mL. 0.1 mL of each working standard solution of Dantrolene Sodium (1-100 µg/mL) was transferred in a series of Eppendorf tubes (Eppendorf-Netheler-Hinz, Hamburg, Germany) containing 0.2 mL of rat plasma, separately. In each flask, 0.1 ml stock solution of Nitrofurazone (20 µg/mL) was added and 0.6 mL of methanol was added for complete precipitation of proteins. Tubes were vortexed for 10 min on vortex mixer and then centrifuged for 15 min at 3000 rpm. The mobile Phase was ethanol: 0.01 M Phosphate buffer pH 3 adjusted with orthrophosphoric acid (65: 35, v/v) using C18 Column (150 mm × 4.6 mm i.d., 3.5 m)at flow rate 1 ml/min wavelength 380 nm.

Blood samples (1 ml) were collected in EDTA coated bottles through retro orbital route during a dosing interval at the following times: 0 (prior to drug administration), 0.5, 1, 2, 4, 6, 10, 12, and 24 h post dose. Samples were centrifuged for 15 min at 3000 rpm to collect plasma and then frozen at –20 °C until analysis. Plasma samples were analyzed for Dantrolene Sodium concentrations by H.P.L.C. under abovementioned conditions.

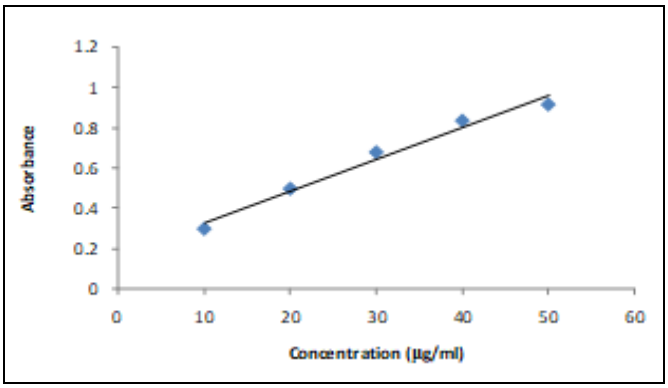

FIG. 1: CALIBRATION CURVE FOR DANTROLENE BY UV SPECTROPHOTOMETRY

RESULTS AND DISCUSSION:

Analytical Method: UV calibration curve: Dantrolene was found to obey Beers law in concentration range of 10-60 µg/ml. the equation of linearity was y = 0.015x + 0.168 and co-efficient of correlation (R^2) was found to be 0.979 **Fig. 1**.

Spherical Agglomeration: Dantrolene sodium drug is poorly water-soluble and possesses poor compaction and flow properties. The agglomerates of Dantrolene sodium were prepared using acrystallo co-agglomeration technique. Dantrolene sodium was crystallized from 1M NaOH, 0.7M HCl, isopropyl acetate system and agglomerated with hydrophilic polymer PEG 6000. Dantrolene sodium is freely soluble in NaOH, but practically insoluble in water. Also it is soluble in isopropylacetate (bridging liquid) which is immiscible with water. Hence, these solvents were selected for the present study. In this process, crystallization of drug was performed by the addition of the anti-solvent phase (water) to drug solution. The addition of bridging liquid (isopropyl acetate) promotes the formation of liquid bridges between the drug crystals of or spheric alagglomerates. The spherically agglomerated crystals are formed by coalescence of these dispersed crystals.

Evaluation of Crystallo Co Agglomerates:

Drug Content: The results of drug content of agglomerates were found to be 98.50%.

Micromeritic Studies: The micromeritic properties such as flow ability of agglomerates represented in terms of the angle of repose, Carr's index and Hausner ratio. The flow behaviour was much improved compared to those of the original drug crystals. Plain Dantrolene sodium crystals have a significantly higher angle of repose (>40) in comparison with the spherical agglomerates, this could be due to their regular shape which hindered in the uniform flow of crystals from the funnel. There as on for the excellent flow ability of spherical agglomerate is the significant reduction in the interparticle friction because of the perfect spherical shape and the larger size of the crystals [16, 17].

Results showed that the angle of repose and Carr's index for Crystallo-co-agglomerates reduced significantly in comparison with the original drug crystals. The Hausner was found to be less than 1.25 indicating improvement in flow properties. These findings proved that the flow-ability of Crystallo-co-agglomerates was preferably improved as compared to pure drug crystals.

Heckel Analysis: Heckel analysis has been used to classify powder compaction behavior and for the interpretation of the mechanism of bonding. MyP is the pressure required to de forma powder or granules and to obtain compacts and is defined as the inverse of slope of the linear portion of the Heckel plot. The slope (k) is an indication of the deformation behavior of the material. With low values of Py, the amount of plasticide formation increases. And when a high value of Py is an indication of the material l compressing behavior is mainly fragmentation. The values obtained from Heckel equation indicated significant low mean yield pressure (Py) of spherical agglomerates (2.7-3.5 ton) than plain Dantrolene sodium (5.95 tonns) indicating improvement in compaction behavior of spherical agglomerates [18].

Dissolution Studies: The dissolution profile is evident that the agglomerates have improved the dissolution rate of Dantrolene sodium significantly the enhancement in dissolution rate of Dantrolene sodium was observed upto 64.7%. There as on for this Faster drug dissolution was linked to the increase in surface area, wetting Dantrolene sodium agglomerates, showed better wettability due to addition of hydrophilic polymer and the porous internal structure resulted in faster dissolution[19].

Saturation Solubility: Dantrolene sodium shows poor aqueous solubility (0.08 mg/ml). Agglomeration technique shows significant improvement in the aqueous solubility of Dantrolene sodium. Incorporation of hydrophilic polymers like PEG 6000 enhances wettability of Dantrolene sodium by the process of hydrophilization which may increases the aqueous solubility of Dantrolene sodium. Also it may increase due to increased surface area, wettability, changes in the crystal forms, structure and surface modification with hydrophilic polymer. There was 8.04 fold increase found in the aqueous solubility of Dantrolene sodium from agglomerates.

Scanning Electron Microscopy (SEM): The Dantrolene sodium particles in the physical mixture were irregular and the shape of prepared agglomerates is uniform and spherical. The reason for the improved flow of agglomerates is the significant reduction in the inter-particle friction because of the nearly spherical shape and the larger size of the crystals **Fig. 2**.

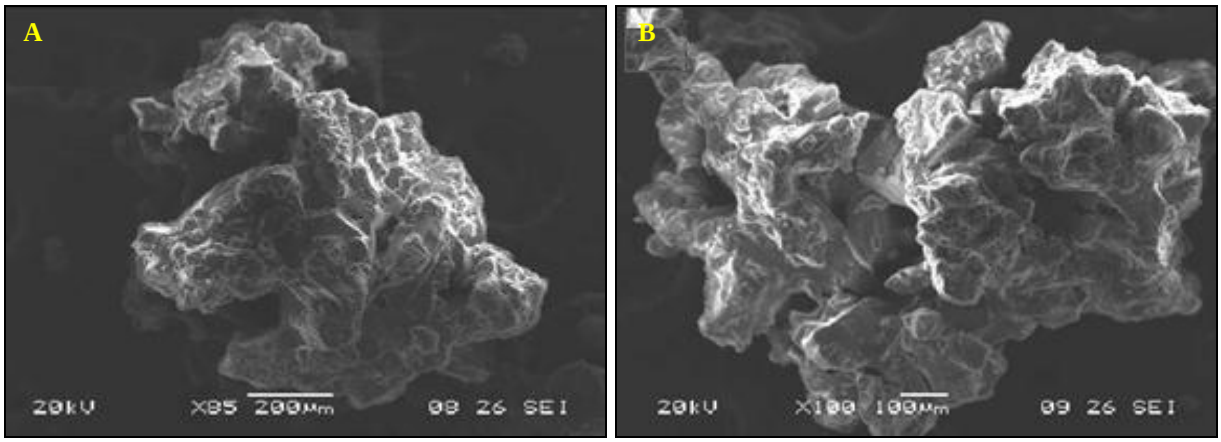

FIG. 2: SCANNING ELECTRON MICROGRAPHS. A DANTROLENE SODIUM POWDER (×85), B AGGLOMERATES OF OPTIMIZED BATCH (×100)

Powder X-Ray Diffraction: The PXRD **Fig. 3** of plain Dantrolene sodium showed intense peaks of crystallinity, whereas the XRD pattern of agglomerates exhibited halo-pattern with less intense and denser peaks compared with plain Dantrolene sodium indicating the decrease in crystallinity or partial amorphization of the drug in its agglomerated form [20].

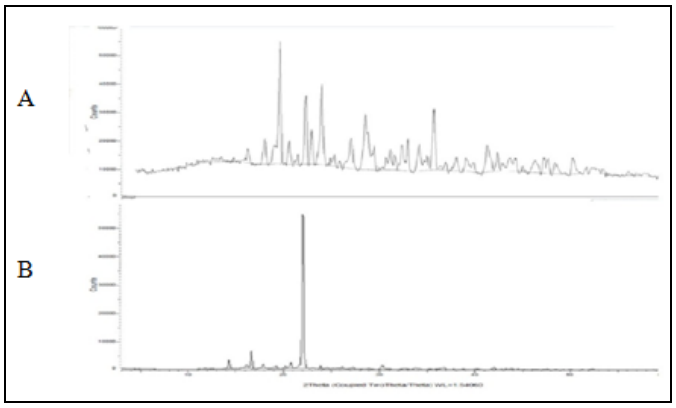

FIG. 3: POWDER X-RAY DIFFRACTOGRAM OF A. DANTROLENE SODIUM AND B. AGGLOMERATES OF DANTROLENE

Optimization using Design Expert, Stat-Ease, Minepollis MN. The experiments were designed to study the effect of three independent variables namely speed of rotation, polymer concentration and amount of bridging liquid at two levels on MYP, % dissolution and Carr index. The traditional approach to developing a formulation is to change one variable at a time but this method it is difficult to develop an optimized formulation, as the method reveals nothing about the interactions among the variable.

Experimental Design: The experiments were designed to study the effect of three independent variables namely speed of rotation, polymer concentration and amount of bridging liquid at two levels on MYP, % dissolution and Carr's index. The traditional approach to developing a formulation is to change one variable at a time. By this method it is difficult to develop an optimized formulation, as the method reveals nothing about the interactions among the variable. Among all the Response surface methods, 2^3 design reduces number of experiments in a3-factor experimental design and requires fewer runs. A 3-factor, 2 level full factorial design would require a total of 8 unique runs. Factorial designs (FD, full or fractional), also known as experimental designs for the first- degree models, are the most popular response surface designs. Full factorial designs involve studying the effect of all factors (n) at various levels (x), including the interactions amongst them with total no. of experiments as xn. The simplest class of FDs involves factors at two levels with factor levels suitably coded. The design is said to be symmetric, if each factor has same number of levels and asymmetric, if the number of levels for each factor differs. The symbol Xn is normally used for representing the factor, where the subscript depicts the number of factor. Factorial design offer following advantages:

1. In the absence of interaction, factorial designs have maximum efficiency in estimating main effects.

2. If interaction exist, factorial designs are necessary to reveal and identify the interactions.

3. Since, factor effects are measured over varying levels of other factors, conclusion applies to a wide range of conditions.

4. Maximum use is made of the data since all main effects and interactions are calculated from all the data.

5. Factorial designs are orthogonal; all estimated effects and interactions are independent of effects of other factors. The batches of 2^3 design and results are represented in the **Table 3**.

Optimization Data Analysis:

TABLE 3: OPTIMIZATION RESULTS FOR DANTROLENE SODIUM

Run	X1 Polymer: drug ratio	X2 Amount of Bridging liquid (ml)	X3 Stirring speed (rpm)	R1 MyP	R2 Dissolution (%)	R3 Carr index (%)
1	0.5:1	4	700	3.1893	88.2	19.6
2	0.5:1	8	1000	3.1233	76.6	18.18
3	1:1	8	1000	3.4014	73.2	21.56
4	1:1	4	1000	3.3699	89.4	21.65
5	1:1	8	700	3.4545	81.2	23.63
6	0.5:1	8	700	3.2662	79.6	19.64
7	0.5:1	4	1000	3.0657	93.6	16.36
8	1:1	4	700	3.3632	87.6	21.62
Dantrolene sodium	-	-	-	-	-	-

*n=3 *i.e.* average of three readings

Influence of Independent Variables:

Influence of Independent Variable on the MYP:

Equation for MYP:

$$MYP = 2.97 - 0.054A - 0.021B - 0.23AB - 0.15AC + 0.043BC - 0.15A$$

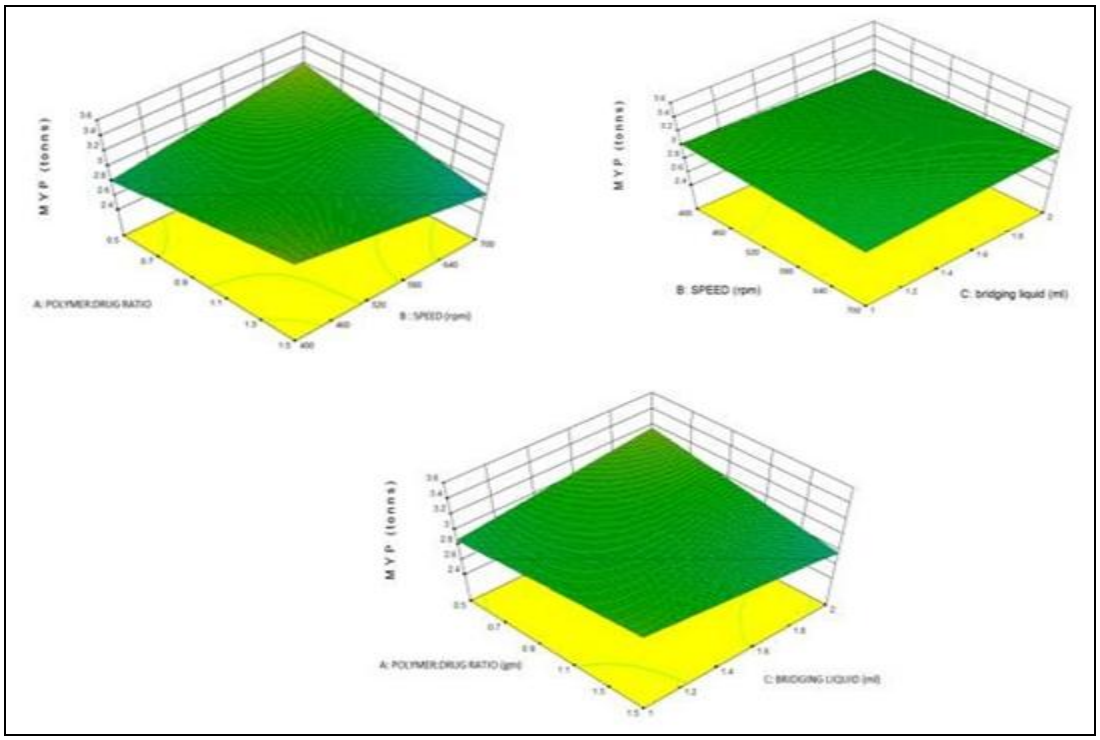

FIG. 4: RESPONSE SURFACE PLOTS FOR MYP

The mean yield pressure values of cystallo co-agglomerates were found to be higher at high polymer and high bridging liquid concentration.

Increase in bridging liquid reduced MYP sharply which may be due to porous agglomerates whereas PEG being soft and plastic in nature gives better compressibility to the formed agglomerates as it undergoes plasticide formation.

The stirring speed did not have appreciable effect on MYP hence was excluded from equation. The combination of low bridging liquid and high stirring speed reduced the MYP as the particle collisions increase at high speed which resulted in smaller particle size and smaller MYP. The binary combination of variables as well as all the three demonstrated a good effect on reducing the MYP **Fig. 4**.

Influence of Independent Variable on the Carr's Index:
Equation for Carr's index:

Carr's Index = + 7.98 − 0.49A + 0.069B − 0.76C − 2.29AB + 1.46AC + 2.01 − 1.18ABC

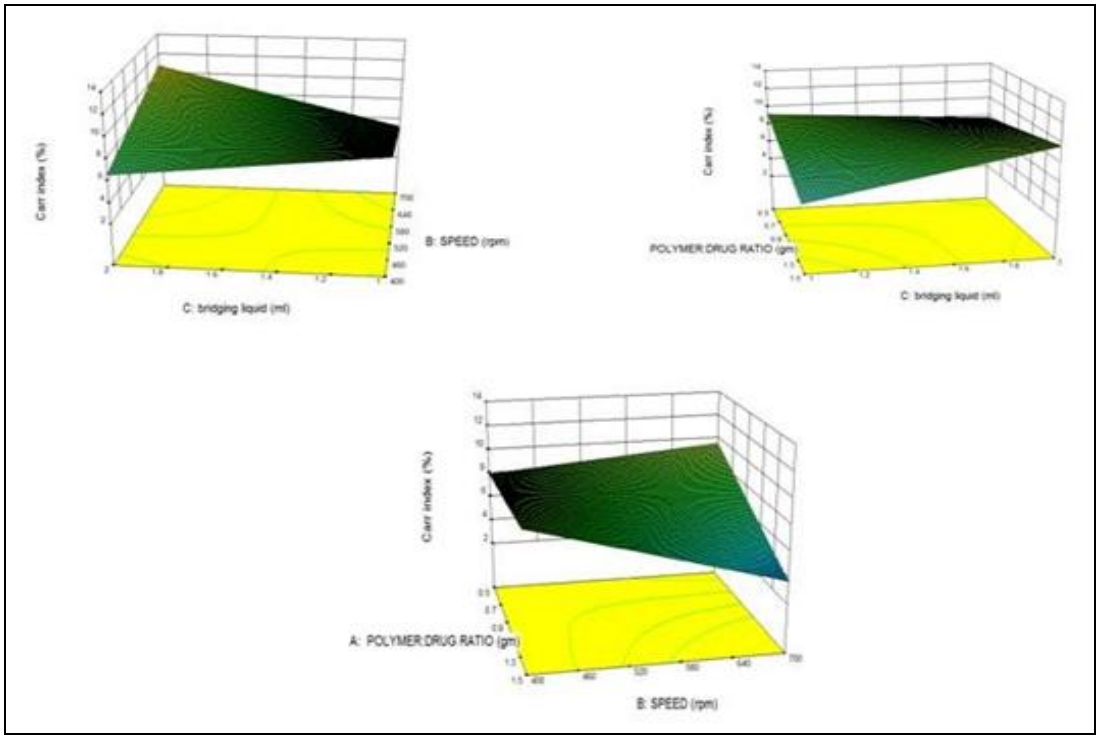

FIG. 5: RESPONSE SURFACE PLOT FOR CARR'S INDEX

Carr's index was reduced by increasing the polymer and increased to some extent by stirring speed. The bridging liquid had highest influence on increasing the Carr's index, Optimum Carr's index values (8.33-14.8%) were seen at high stirring speeds and bridging liquid combination, the values declined with decrease in either of the variables. Whereas low polymer and high bridging liquid combinations exhibited good Carr's index **Fig. 5**.

Influence of independent variable on the Dissolution:
Equation for Dissolution:

Dissolution = + 33.85 − 7.87A − 0.80B + 1.21C − 6.26AB + 0.44AC + 9.42 − 3.50ABC

The dissolution is most coveted characteristic of a drug material; dissolution of Dantrolene sodium was highly reduced by increasing polymer content as agglomerates formed were sticky in nature. The low stirring speeds which produce bigger agglomerates may also reduce the dissolution. The higher polymer: drug ratio and low bridging lead to significant reduction in dissolution. High bridging liquid and high stirring speed show increase in dissolution. Also a combination of low polymer: drug ratio and high stirring speed lead to increase in dissolution. Incorporation of PEG causes faster consolidation and yields particles with lower tortuosity and hence batches containing PEG at higher levels exhibits lower release of drugs **Fig. 6**.

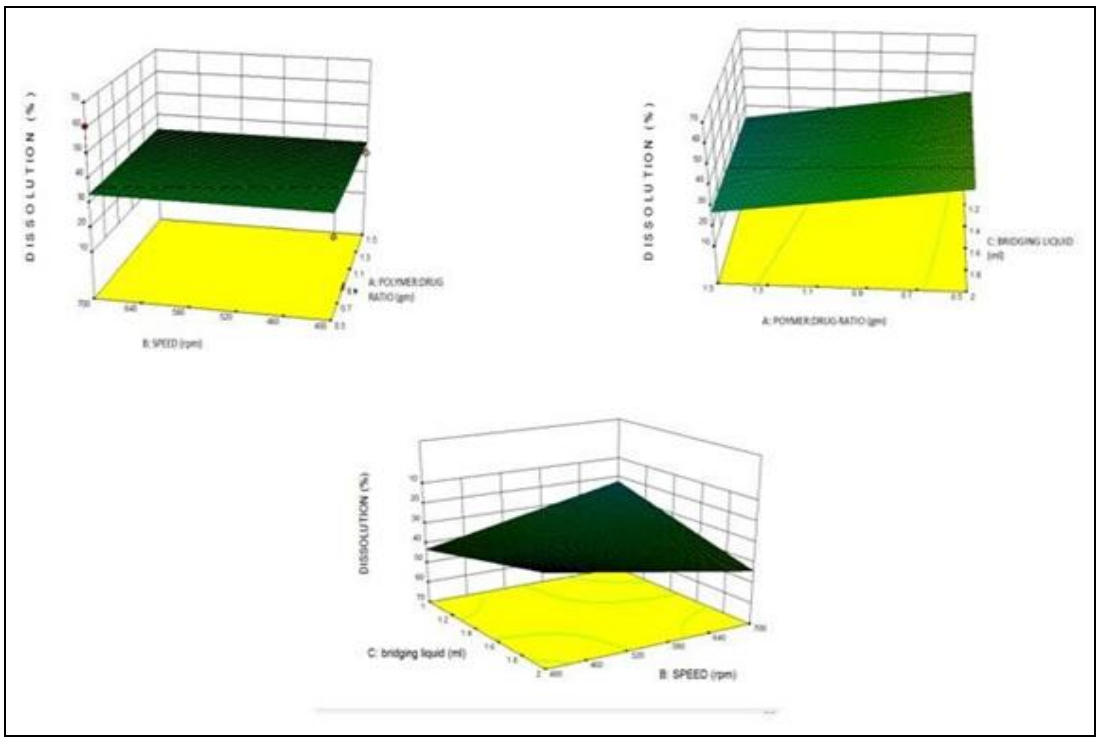

FIG. 6: RESPONSE SURFACE PLOT FOR DISSOLUTION

Optimization and Data Analysis: The formulations prepared as per the experimental design were evaluated and the analysis of experimental results was done by using the Design Expert. The ANOVA, P-value and model F-value for Carr's index, % Dissolution and MYP were obtained **Table 4**.

TABLE 4: ANOVA OUTPUT OF THE 2^3 DESIGN FOR OPTIMIZATION OF CRYSTALLOCOAGGLOMERATES

Sr. no	Outcomes	Carr's Index %	Dissolution %	MYP Tonne
1	F value	85.23	54.31	66.39
2	P value	0.0096	0.0001	0.0092
3	R^2 value	0.993	0.981	0.973

F value for models was found to be high which indicated that the models were significant. P value less than 0.05 indicated that the model terms were significant. High R^2 values indicated good agreement between formulation variables and response parameters. Thus, the models can be used to predict the values of the response parameters at selected values of formulation variables within the design space.

The solution provided by the Design Expert software on the basis of desirability function was, polymer: drug ratio concentration (0.5:1), speed of rotation (700 rpm) and amount of bridging liquid (2 ml) and had desirability value of 1 to obtain optimum parameters for the preparation of Spherical agglomerates **Table 5**.

TABLE 5: PROPERTIES OF SPHERICAL AGGLOMERATES (N=3)

System/ parameters	Hausner ratio	Carr's Index	% dissolution	MyP ton
Dantrolene	1.6	60	8.1	5.74
Spherical agglomerates	1.2	16.07	89.26	3.58

PXRD: The PXRD scan of plain Dantrolene showed intense peak so of crystallinity, whereas the XRD pattern of agglomerates exhibited halo pattern with less intense and denser peaks Compared with plain Dantrolene indicating the decrease in crystallinity or partial amorphization of the drug in its agglomerated form.

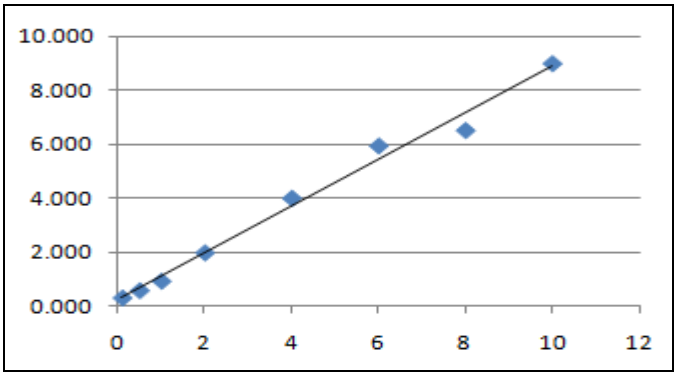

FIG. 7: CALIBRATION CURVE FOR DANTROLENE SODIUM IN PLASMA

$y = 0.8685x + 0.2199 R^2 = 0.9888$

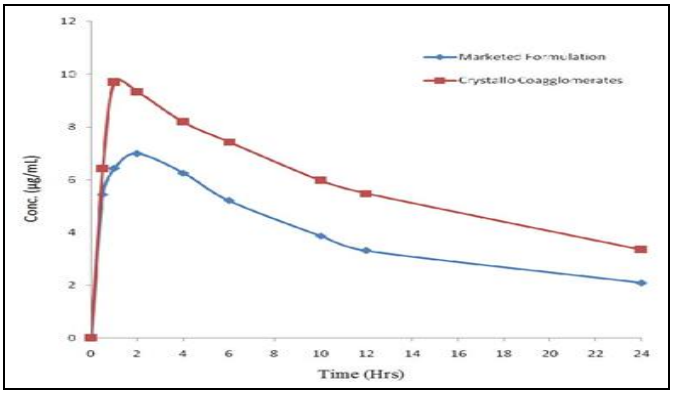

FIG. 8: PHARMACOKINETIC PROFILE FOR DANTROLENE SODIUM MARKETED FORMULATION AND DANTROLENE SODIUM AGGLOMERATES

TABLE 6: SUMMARY OF PHARMACOKINETIC ANALYSIS

	Marketed Formulation	Agglomerates	% (Test/Ref)
Cmax (mcg/mL)	6.988	9.696	138.75
AUC (0-24h)	145.52	217.203	149.26
tmax (hr)	2.0	1.0	

There is marked increase in AUC (24 µg/mL/h) with significant decrease in t_{max}. Also there is increase in C_{max} value indicate crystallo agglomeration has improved the formulation in terms of fast action.

CONCLUSION: The crystallo co agglomerates of Dantrolene a BCS class II drug offer a practical way to overcome the limitations such as poor dissolution, flow and compression characteristics. The agglomeration process can be optimized using a factorial design with respect to parameters like stirring speed, polymer concentration and bridging liquid to obtain agglomerates with suitable performance characteristic such as minimum yield pressure, Carr's index and dissolution.

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CONFLICT OF INTEREST: Authors declare no conflict of interest.

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