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FORMULATION AND EVALUATION OF SPHERICAL CRYSTALS OF INDOMETHACIN FOR THE IMPROVEMENT OF SOLUBILITY AND MICROMERITIC PROPERTIES

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Keywords:

Crystalloco-agglomeration, Indomethacin, Optimization, Compression, Dissolution

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ABSTRACT: Indomethacin, an anti-inflammatory drug, exhibits poor water solubility and flow properties. Spherical agglomerates were prepared by crystallo-co agglomeration technique. Crystallization medium used for spherical agglomerates of Indomethacin consisted of acetone (good solvent); water (poor solvent); dichloromethane (bridging liquid). HPMC, PVP and PEG6000 this polymer were used in the agglomeration process. Spherical agglomerates were characterized by DSC, IR, XRD, and SEM. Micromeritic, dissolution behavior and compression studies were carried out. For optimization study Box Behnken Design used. Heckle plot studies showed low mean yield pressure and a low value indicating excellent compressibility and compatibility of agglomerates. Process variables such as an amount of bridging liquid, stirring speed and polymer ratio were optimized. The dissolution profile of the spherical agglomerates was compared with pure Indomethacin. Spherical agglomerates exhibited decreased crystallinity and improved micromeritic properties. The dissolution of the spherical agglomerates was improved compared with pure Indomethacin sample.

INTRODUCTION: Oral route of drug administration has wide acceptance and hence up to 50-60% of total dosage forms are administered orally. The most popular dosage forms being tablets and capsules [1]. This technique was first proposed by Kawashima Y *et al.*, Spherical crystallization was defined "it as an agglomeration process that transforms crystals directly into compact spherical forms during the crystallization. It also enables co-precipitation of drug and encapsulating polymer in the form of spherical particle [2, 3].

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Spherical crystallization is an effective alternative to improve the dissolution rate of drugs [4]. This can be achieved by various methods such as spherical agglomeration, quasi-emulsion solvent diffusion, Ammonia water method, Crystallo-Co agglomeration and neutralization method [5]. Agglomerates exhibit improved secondary characteristics, like flowability and compressibility, so that direct tableting or coating is possible without further processing (mixing, agglomerates, sieving, *etc.*) [6, 7].

Apart from the particle size enlargement, this technique has also been applied for various purposes such as taste masking and particle size enlargement [4, 8]. The main purpose of this work was to improve the solubility, dissolution rate, micrometric properties of Indomethacin by Crystallo-co agglomeration technique.

Crystallo-co-agglomeration (CCA) technique involves simultaneous crystallization and agglomeration of drug/s with/without excipient/s from the suitable solvent and bridging liquid by addition of a non-solvent.

The spherical agglomerates obtained by CCA can be used as intact beads (encapsulated spansules), or directly compressible tablet intermediates are having satisfactory micrometric (flowability), mechanical (friability, crushing), compressional (compressibility, compatibility) and drug release properties [9]. Spherical agglomeration is a process of formation of aggregates of crystals held together by liquid bridges. The agglomerates are formed by agitating the crystals in a liquid suspension in the presence of the binding agent. The binding liquid should be immiscible in the suspending medium but capable of cementing the particles to be agglomerated. The properties of the particles so designed vary greatly as compared to the fine crystalline material. These agglomerates were found to have good flowability and compressibility. This technique can also be exploited to increase solubility, dissolution and hence bioavailability of poorly soluble drugs [10, 11]. In the process, Indomethacin was crystallized from acetone, dichloromethane, and water using various polymers. Acetone was used as a good solvent. Dichloromethane served as the bridging liquid and aqueous phase as the bad solvent. The agglomerates obtained were evaluated using differential scanning calorimetry (DSC), scanning electron microscopy (SEM), powder x-ray diffraction (PXRD), and tableting and drug release properties.

MATERIAL AND METHOD: Indomethacin (IM) was generously supplied as a gift sample from Lupine Research Park, Pune (India). Polyvinyl pyrrolidone (PVP K30), hydroxypropyl methylcellulose (HPMC), Polyethylene glycol 6000 (PEG 6000) were obtained from Lobachemi Pvt. Ltd. Solvents such as Acetone, dichloromethane were of analytical grade.

Method: [12] The spherical crystallization was carried out by using three partially miscible solvents, *i.e.* good solvent (acetone), bridging liquid (dichloromethane) and poor solvent (distilled water). Indomethacin was dissolved in acetone and added to an aqueous polymeric solution of HPMC and under continuous stirring. The dichloromethane was added dropwise. After continuous stirring, the spherical agglomerates were formed. This mixture was agitated under 600, 900, 1200 rpm. The drug-polymer ratios used for making agglomerates were 1:0.25, 1:0.5, 1:0.75 **Table 1**.

TABLE 1: CODED VARIABLES THEIR TRANSLATION INTO ACTUAL LEVELS AND RESPONSE VARIABLE WITH CONSTRAINTS

Independent variables	Symbol	Levels		
		-1	0	1
Stirring Speed (rpm)	A	600	900	1200
Polymer Concentration (g)	B	0.25	0.75	0.75
Bridging liquid (ml)	C	2	4	6
Dependent variables	Units		Constraint	
Y1 = Dissolution	%		Maximize	
Y2 = Carr's index	%		Minimize	
Y3 = MYP	Ton		Minimize	

Micromeritic Properties: Flowability assessment was done by the angle of repose, Carr's compressibility index (CCI) and Hausner's ratio (HR). The angle of repose was determined using the 'fixed funnel free-standing cone method.' CCI and HR of agglomerates were determined from the values of bulk density and tapped density [13].

Heckle Plot: For Heckle plot pallets were made by using 200 mg spherical agglomerates and applying various pressures, thickness, diameter, and hardness of pallets were measured. Using Heckle plot software mean yield pressure (MYP) value calculated.

Drug Content: Spherical agglomerates (50 mg) was triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml five milliliters of this solution was mixed with equal volumes of methanol and phosphate buffer pH 7.2 to produce 100 ml. The absorbance of the resulting

solution was measured at 320 nm. Drug content was determined from the standard plot.

Fourier Transforms Infrared Spectroscopy (FTIR): The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033. Samples were dispersed in KBr powder, and the pallets were made by applying 5-ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-Ray Powder Diffraction (XRPD) Study: The XRPD patterns of the samples were monitored with an x-ray diffractometer (Philips PW 1729, Analytical XRD, Holland) using Ni-filtered CuK(α) radiation (intensity ratio (α1/ α2): 0.500), voltage of 40 KV, current of 30 mA and receiving slit of 0.2 inches. The samples were analyzed over a 2θ range of 5.010-39.990º with scanning step size of 0.020º (2θ) and scan step time of one second.

Scanning Electron Microscopy (SEM): Scanning electron microscopic photographs were obtained to identify and confirm spherical nature and morphological characters of the crystals.

Dissolution Studies of Agglomerates: The dissolution of IM sample and spherical agglomerates and was determined by using USP dissolution apparatus -type II (Lab India DS 8000). Dissolution medium (750 ml) consisted of (one part of 7.2 Phosphate buffer and four parts of water) was used, and 10 ml of dissolution medium was withdrawn at every 10 min interval for 1 h. The amount of dissolved drug was determined using UV spectrophotometric method (Lab India UV 3000) at 320 nm.

Pharmacokinetic Analysis: Standard stock solution of Indomethacin and Mefenamic Acid were prepared by using concentration 1, 5, 10, 20, 40, 60, 80 and 100 µg/mL. Mefenamic Acid solution standard solution of concentration 50 µg/mL was prepared on suitable dilution. 0.1 mL of each standard working solution of Indomethacin (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 Mefenamic Acid (50 µg/mL) was added, and 0.6 mL of methanol was added for complete precipitation of proteins. Tubes were vortexed for 10 min on the vortex mixer and then centrifuged for 20 min at 2500 rpm. The supernatant solution was directly injected on a chromatographic column. The peak area ratios of Indomethacin to Mefenamic acid were calculated, and the calibration curve was plotted of response factor against the concentration of the drug. Blood samples (1 ml) were collected in EDTA coated bottles through retro-orbital route during a dosing interval at the following times: 0 (before 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 Indomethacin concentrations by H.P.L.C. under above-mentioned conditions.

RESULTS AND DISCUSSION: Spherical agglomeration technique was used for the preparation of Indomethacin spherical agglomerates. Spherical crystallization system contained the good solvent, bad solvent and bridging liquid. The selection of these solvent depends upon miscibility of the solvent and solubility of Indomethacin. So for CCA acetone, water and dichloromethane selected as a good solvent, bad solvent and bridging liquid. Indomethacin shows poor flow properties, and solubility and spherical agglomeration are known to significantly improve the flow properties of drug and dissolution. The agglomerates prepared using an optimum amount of HPMC (0.5:1) show adequate sphericity and mechanical strength.

TABLE 2: COMPARISON OF PROPERTIES OF INDOMETHACIN AND SPHERICAL AGGLOMERATES

	Bulk density mg/ml	Tap density mg/ml	CI %	Hausner's ratio	Angle of repose	Dissolution %	Drug content %	Heckel (MYP) tons
Indomethacin	0.25 ±0.17	0.37 ±0.14	32.43 ±0.68	1.44 ±0.010	53.67 ±0.62	31.6 ±0.18	-	3.75 ±0.12
Spherical agglomerates	0.41 ±0.12	0.49 ±0.16	16.32 ±0.48	1.2 ±0.006	23.62 ±0.48	85 ±0.14	95 ±0.48	3.18 ±0.09

Optimization Study [14]: For optimization study Box-Behnken design was used concentration of HPMC, stirring speed and quantity of bridging liquid were selected as factors. The level of HPMC concentration was selected 0.25 g, 0.5 g, and 0.75 g. The levels of stirring speed were selected to be 600, 900 and 1200 rpm. And the level for bridging liquid was selected to be 2, 4 and 6 ml. Carr's index, % dissolution, and MYP value were selected as the response. Variables and their levels used in Box–Behnken experimental design **Table 3**.

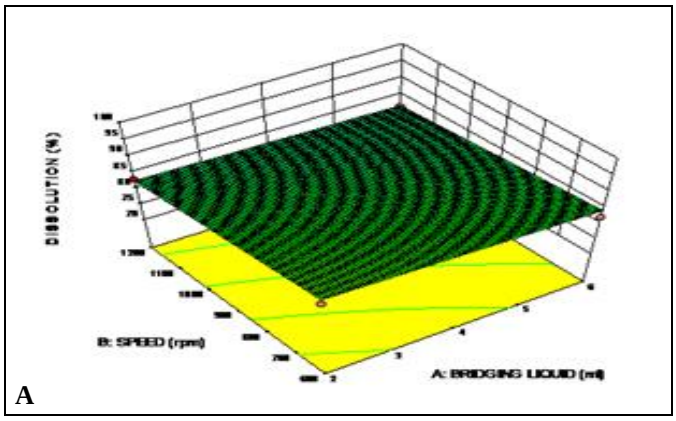
TABLE 3: THE PARAMETER EMPLOYED IN BOX BEHNKEN DESIGN FOR OPTIMIZING SPHERICAL CRYSTALS OF INDOMETHACIN AND RESPONSE VARIABLES

Batch code	Bridging liquid (ml)	Speed (rpm)	Polymer (gm)	Dissolution (%)	Carr's Index (%)	Heckel MYP (tons)
F1	6	900	0.25	91.6 ± 0.14	15 ± 0.68	3.06578 ± 0.12
F2	2	900	0.25	90 ± 0.18	14.7 ± 0.73	3.01989 ± 0.10
F3	2	900	0.75	81.6 ± 0.15	21.05 ± 0.55	3.36994 ± 0.15
F4	4	1200	0.25	88.2 ± 0.23	16 ± 0.63	3.12337 ± 0.08
F5	2	1200	0.5	83.2 ± 0.18	15.5 ± 0.85	3.26623 ± 0.06
F6	6	1200	0.5	81.6 ± 0.19	16.66 ± 0.52	3.3 ± 0.10
F7	6	900	0.25	91.6 ± 0.10	15 ± 0.40	3.06578 ± 0.12
F8	4	600	0.75	75 ± 0.24	19.04± 0.85	3.50362 ± 0.10
F9	4	600	0.25	96.6 ± 0.10	14.28 ± 0.35	2.92463 ± 0.06
F10	4	1200	0.75	73.2 ± 0.18	17.85 ± 0.46	3.43326 ± 0.12
F11	2	600	0.5	85 ± 0.15	15.38 ± 0.62	3.18934 ± 0.09
F12	6	600	0.5	82.2 ± 0.14	17.24 ± 0.54	3.05766 ± 0.10

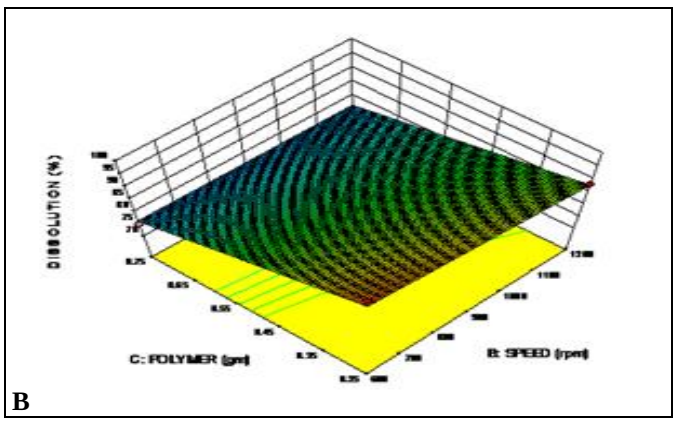
Influence of Independent Variables on the Dissolution Study: The value of correlation coefficient, R^2 for dissolution was found to be 0.9050 which indicated a good fit of the model.

Equation for Dissolution Study:

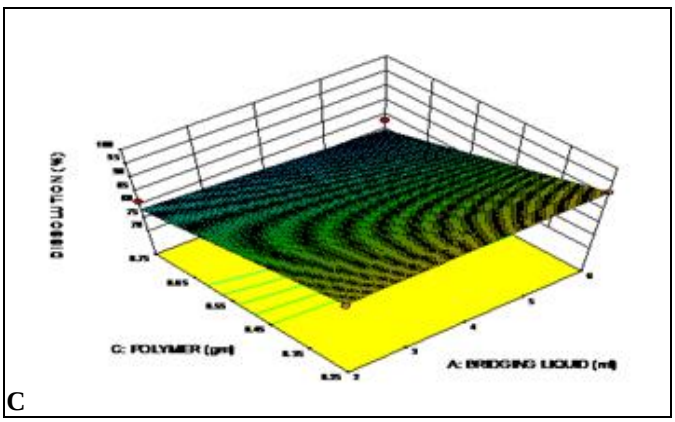
Dissolution = +83.87-0.78*A-1.58B-7.30*C+030* AB-1.25*AC+1.65*BC



A



B



C

FIG. 1: THE 3-D RESPONSE SURFACE PLOTS SHOWING EFFECT OF VARIOUS PROCESS PARAMETERS ON DISSOLUTION

Fig. 1 illustrates the interplay between various factors studied for their effect on dissolution. The dissolution equation shows that the speed, bridging liquid and polymer decrease with increase in dissolution. The combined effect of polymer and liquid shows that decrease with increase in dissolution. The combined effect of bridging liquid and speed increases then dissolution slightly increases. Also combined effect of speed and polymer indicate that increase with an increase in dissolution **Table 3**.

At high polymer ratio, the lumps were formed, and viscosity increased which caused the sticky product. At high-speed stirring caused the breaking of particles.

Influence of Independent Variable on the Carr's Index: The value of correlation coefficient, R^2 for Carr's Index was found to be 0.7746 which indicated a good fit of the model.

The equation for Carr's Index:

Carr's Index = +16.90+0.30*A-3.750E-003*B+ 2.25*C

Fig. 2 illustrates the interplay between various factors studied for their effect on Carr's Index. The equation shows that speed, bridging liquid and polymer increase with an increase in Carr's Index. Hence, low concentration of polymer and low speed produced a better result for Carr's index.

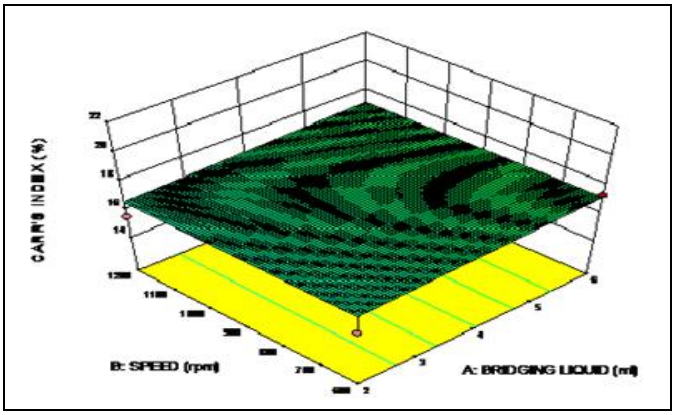


FIG. 2: THE 3-D RESPONSE SURFACE PLOTS SHOWING EFFECT OF VARIOUS PROCESS PARAMETERS ON CARR's INDEX

Influence of Independent Variables on the MYP: The value of correlation coefficient, R^2 for MYP was found to be 0.9533 which indicated a good fit of the model.

Equation for MYP:

MYP = +3.22+0.056*B+0.20*C+0.041*AB-0.067*BC

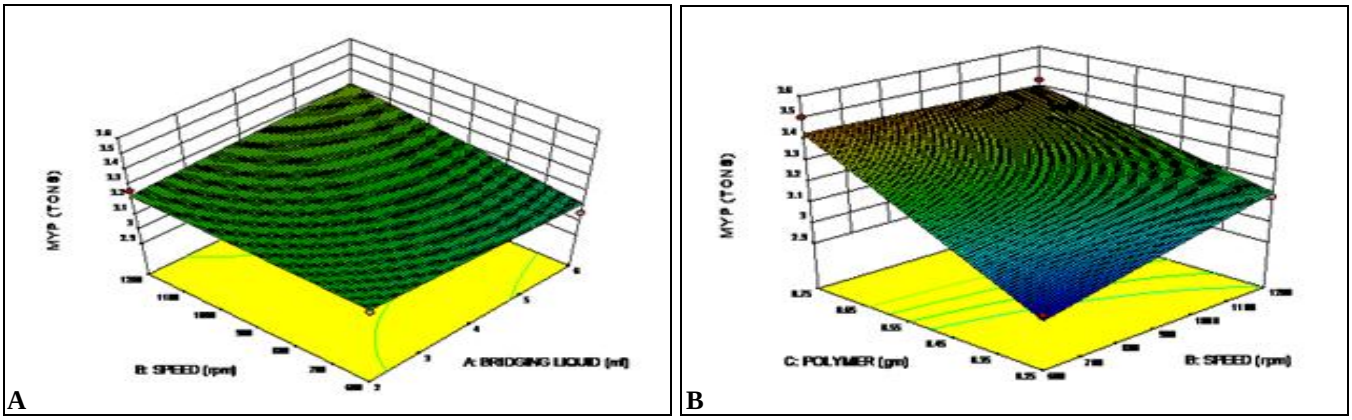


FIG. 3: THE 3-D RESPONSE SURFACE PLOTS SHOWING EFFECT OF VARIOUS PROCESS PARAMETERS ON MYP

Fig. 3 illustrates the interplay between various factors studied for their effect on MYP value. The equation indicates that the effect of polymer and speed increase with increases the MYP value. The combined effect of speed and bridging indicates that increase with increases the MYP value. Means at the low value it indicates that good compressibility property.

Micromeritics Properties: All micromeritic properties indicated in **Table 4**. It indicates that bulk density, tap density, the angle of repose, Hausner's ratio, drug content, and particle size. All F1 to F12 batches compared with the indomethacin drug powder properties. In all 12 batches F9 batch indicates the very good result.

TABLE 4: MICROMERITIC PROPERTIES AND DRUG CONTENT OF PREPARED AGGLOMERATES FROM BOX BEHNKNEN DESIGN

Batch code	Bulk Density mg/ml	Tap Density mg/ml	The angle of repose (°)	Hausner's ratio	Drug content %	Particle Size (µm)
F1	0.34 ± 0.015	0.40 ± 0.014	26.56 ± 0.54	1.17 ± 0.009	90 ± 0.36	210.20 ± 8.42
F2	0.30 ± 0.012	0.35 ± 0.012	25.01 ± 0.48	1.16 ± 0.007	91.16 ± 0.45	282.8 ± 6.54
F3	0.30 ± 0.010	0.38 ± 0.015	27.47 ± 0.64	1.26 ± 0.010	88.3 ± 0.85	265.6 ± 9.33
F4	0.21 ± 0.014	0.25 ± 0.017	23.62 ± 0.58	1.19 ± 0.006	94.16 ± 0.56	131.3 ± 6.40
F5	0.30 ± 0.018	0.35 ± 0.010	23.62 ± 0.49	1.16 ± 0.07	90 ± 0.76	254.18 ± 8.62
F6	0.30 ± 0.015	0.36 ± 0.012	25.34 ± 0.62	1.2 ± 0.008	89.60 ± 0.68	202.77 ± 7.35
F7	0.34 ± 0.010	0.40 ± 0.010	23.62 ± 0.52	1.17 ± 0.006	92.5 ± 0.76	185.64 ± 6.68
F8	0.34 ± 0.015	0.42 ± 0.017	27.64 ± 0.48	1.23 ± 0.009	88.30.38 ± 0.62	302.73 ± 6.40
F9	0.42 ± 0.012	0.49 ± 0.010	22.61 ± 0.42	1.16 ± 0.005	95.83 ± 0.46	164.22 ± 5.01
F10	0.23 ± 0.014	0.28 ± 0.012	25.34 ± 0.65	1.21 ± 0.010	89.60 ± 0.42	214.2 ± 9.45
F11	0.33 ± 0.12	0.39 ± 0.014	26.56 ± 0.63	1.18 ± 0.007	87.5 ± 0.72	154.22 ± 8.70
F12	0.24 ± 0.017	0.29 ± .015	23.19 ± 0.44	1.20 ± 0.008	89.60 ± 0.42	162.79 ± 9.15

Scanning Electron Microscopy [15]: Particles of pure drug sample are of the smallest size, and they have irregular shapes. Drug-polymer agglomerates prepared were spherical with a rough surface. Sizes of prepared agglomerates were larger than the pure drug Indomethacin.

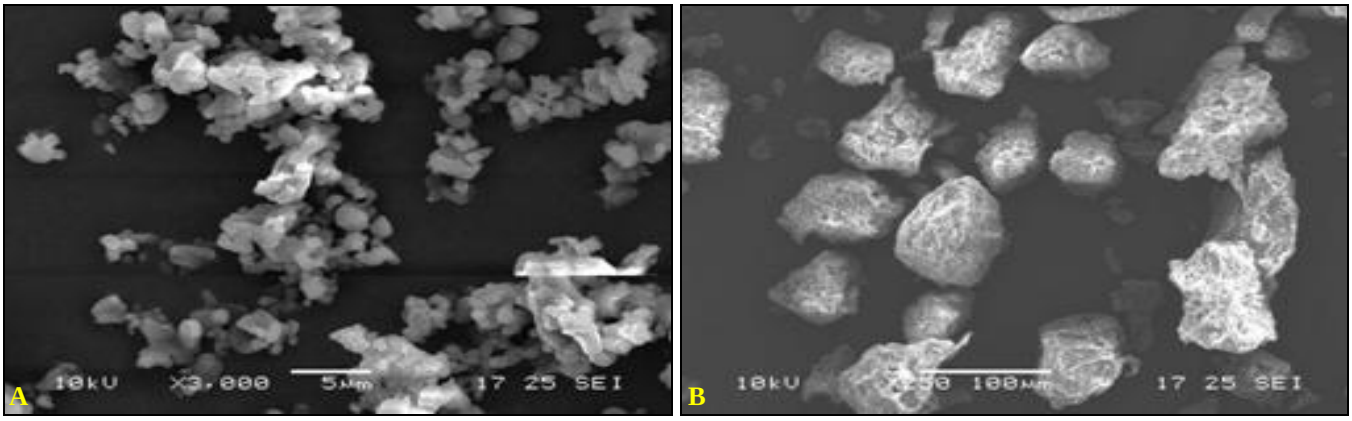


FIG. 4: SEM OF INDOMETHACIN PURE DRUG SAMPLE (A), AND F9 BATCH HPMC +DRUG AGGLOMERATES (B)

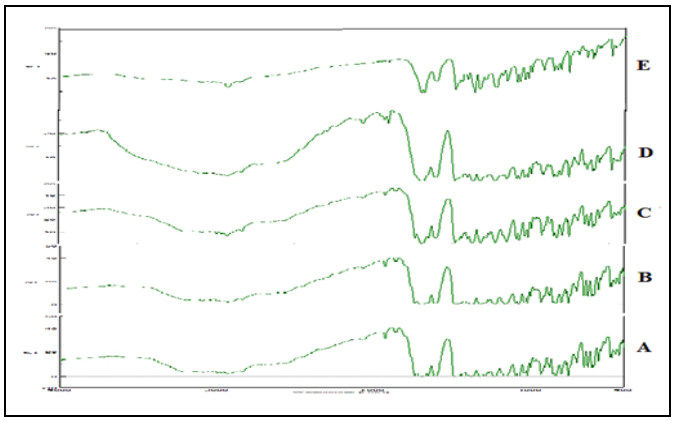


FIG. 5: COMPARISON BETWEEN FTIR SPECTRA OF PURE DRUG (A), PHYSICAL MIXTURE OF INDOMETHACIN + PEG 6000(B), PHYSICAL MIXTURE OF INDOMETHACIN + PVP(C), PHYSICAL MIXTURE OF INDOMETHACIN + HPMC (D) AND F9 BATCH (E)

FTIR Spectroscopy Study: The characteristic peaks of the drug *viz*. C-H stretch (3079.76), C=C stretch (1607.38), C-O stretch (1252.54), C=O (1705), C-Cl stretch (752.102), C-H stretch (2852.2) & C=O stretch (1691.37) were retained with trivial shifts in wave numbers as seen in **Fig. 5**. There were neither any shifts nor disappearances of characteristic peaks. Appearances of any new peaks were not observed, suggesting that interaction between Indomethacin and other excipients or degradation in drug molecule did not take place. Hence, drug excipients compatibility was established signifying no interaction between the drug and other excipients.

PXRD Study: Investigation of the X-ray diffractogram **Fig. 6** revealed some changes in the location of the peak of different crystal forms of agglomerates with respect to Indomethacin. Change in the intensity of peak, which indicates a different arrangement of molecule hence confirming the development of different polymorphic form. Also,

it indicates that the decrease in intensity of agglomerates peak, so a decrease in crystallinity of peak.

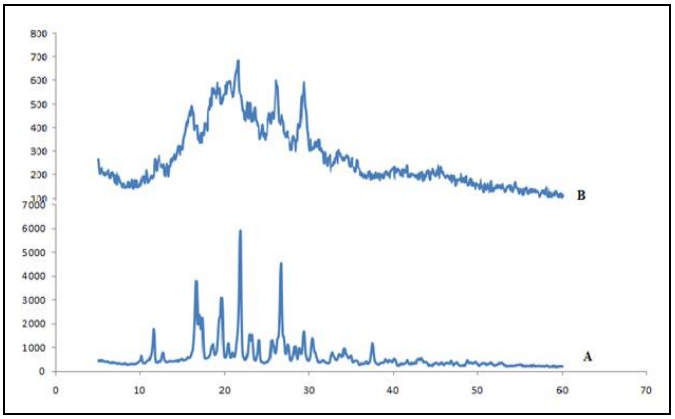


FIG. 6: PXRD STUDIES OF PURE DRUG (A) AND F9 BATCH (B)

Dissolution Study: In the dissolution study, the drug release between 73.2 ± 0.18% to 96.6 ± 0.10%) of spherical agglomerates (F1 to F12) compared with Indomethacin (31.6 ± 0.18%).

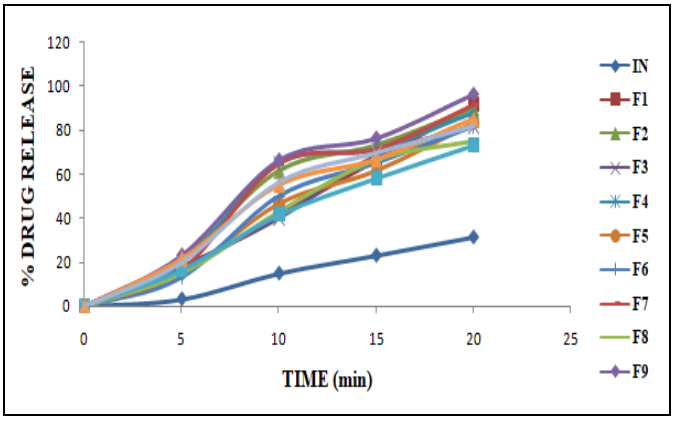


FIG. 7: DISSOLUTION PROFILES OF TRIAL RUNS OF OPTIMIZATION DESIGN

Pharmacokinetic Study: The AUC and C_{max} of Indomethacin agglomerates significantly exceeded that from Indomethacin marketed formulation while the t_{max} did not change appreciably; this is attributed to faster dissolution and better absorption of indomethacin from agglomerates **Fig. 8** and **Table 5**.

TABLE 5: PHARMACOKINETIC DETAILS FOR INDOMETHACIN

	Marketed Formulation	Agglome -rates	% Improvement (Test/Ref)
C_{max} (mcg/mL)	4.472	6.593	47.43
AUC (0-24h)	83.119	134.406	61.70
t_{max} (hr)	2.0	1.0	

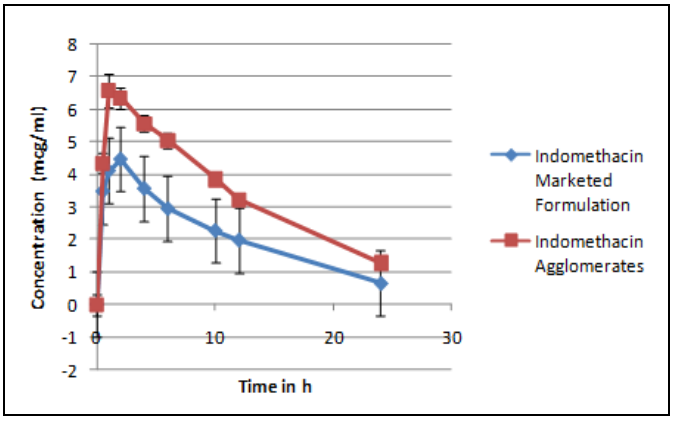


FIG. 8: PHARMACOKINETIC PROFILE FOR INDOMETHACIN MARKETED FORMULATION AND INDOMETHACIN AGGLOMERATES

CONCLUSION: Indomethacin agglomerates were successfully prepared by spherical agglomeration using HPMC. Spherical agglomerates exhibited improved micromeritic properties compared to pure drug. Formulation F9 was selected as optimized formulation which shows better result with respect to percent drug release (96.6 ± 0.10), MYP value (2.92 ± 0.06) and Carr's index (14.28 ± 0.35%) when compared to other formulation, hence this technique can be used for formulation of tablets of Indomethacin by direct compression with directly compressible excipients.

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CONFLICT OF INTEREST: Authors declare no conflict of interest.

REFERENCES:

1. Yadav AV: Novel approach to formulate ß-cyclodextrin complexed mouth dissolving tablet of metronidazole and its *in-vitro* evaluation. Journal of Pharmacy Research 2010; 3(3): 662-67.
2. Di Martino P, Di Cristofaro R, Barthelemy C, Joiris E, Palmieri-Filippo GP and Sante M: Improved compression properties of propyphenazone spherical crystals. International Journal of Pharmaceutics 2000; 197(1): 95-106.
3. Bharti N, Bhandari N, Sharma P, Singh K and Kumar A: Spherical Crystallization: A Novel Drug Delivery Approach. Asian Journal of Biomedical and Pharmaceutical Sciences 2013; 3(18): 10-6.
4. Goczo H, Szabo RP, Nezdei MH and Farkas B: Development of spherical crystals Acetyl salicylic acid for direct tablet making. Chemical and Pharmaceutical Bulletin 2000; 48(12): 1877-1881.
5. Kawashima Y: Archives of Pharmacal Research 1984, 7: 145-151.

6. Wells J: Pharmaceutical Preformulation, The physio-chemical Properties of Drug substances in: M. E. Aulton (ed), Pharmaceutics-the science of dosage forms design. 2nd ed. Churchill Living-Stone, CN, London 2002: 113-138.
7. Morshima K, Kawashima Y, Takeuchi H and Hino T: Tabeletting properties of bucillamine agglomerates prepared by the spherical crystallization technique. Int J Pharm 1994; 105: 11-18.
8. Di Martino P, Barthelemy C, Piva F, Joiri E, Palmieri GF and Martelli S: Drug Development and Industrial Pharmacy 1999; 25: 1073.
9. Paradkar AR, Pawar AP and Jadhav NR: Crystallo-co-agglomeration technique: A novel particle engineering technique. Asian Journal of Pharmaceutics 2010; 4-10.
10. Sano A, Kuriki T, Handa T, Takeuchi H and Kawashima Y: Journal of Pharmaceutical Sciences 1987; 76: 471.
11. Sano A, Kuriki T, Kawashima Y, Takeuchi H, Niwa T and Hino T: Chemical and Pharmaceutical Bulletin 1990; 40: 3030.
12. Paradkar AR, Pawar AP and Jadhav NR: Crystallo-co-agglomeration: A novel particle engineering technique. Asian Journal of Pharmaceutics 2010; 5-10.
13. Lachman L and Liberman HA: The Theory and Practice of Industrial Pharmacy, CBS Publication 2009: 171-196, 293-345.
14. Rahate NB, Bodhankar MM and Dhoke PN: Crystalo-co-agglomeration: A novel technique to improve flow and compressibility. Journal of Drug Delivery & Therapeutics 2013; 3(4): 178-183.
15. Khan K, Sarfaraz MD and Doddayya H: Design and evaluation of Aceclofenac fast dissolving tablets by crystallo-co-agglomeration technique. International Journal of Pharmacy and Pharmaceutical Sciences 3(4): 116-23.

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