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Research Article

APPLICATION OF SPHERICAL AGGLOMERATION TECHNIQUE TO IMPROVE MICROMERITIC PROPERTIES AND DISSOLUTION CHARACTERISTICS OF NABUMETONE

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ABSTRACT
The present work is aimed to enhance the solubility and dissolution rate of Nabumetone, 4-(6-methoxy-2-naphalenyl)-2-butanone water insoluble anti-inflammatory drug by spherical agglomeration technique using a solvent change method consisting of acetone, water and dichloromethane as solvent, non solvent and bridging liquid respectively. The hydrophilic polymers like poly vinyl pyrrolidone K-30 (PVP) and sodium alginate were used in the agglomeration process. Infrared (I.R) spectroscopic studies, Differential scanning calorimetery (DSC) and Scanning electron microscopy (SEM) were used for characterization of pure drug and its agglomerates. The I.R spectroscopy revealed that there is no chemical interaction between drug and polymers, also indicated that no chemical changes in the crystallized agglomerates .The agglomerates exhibited significantly improved solubility, dissolution rate and micromeritic properties (angle of repose, Carr's index, bulk density, tapped density. Hausner's ratio) compared with pure drug Nabumetone. The aqueous solubility and dissolution rate of the drug from spherical agglomerates was significantly ($p < 0.05$) increased (nearly two times). SEM studies revealed that the agglomerates possess a good spherical shape. The study revealed that Micromeritic Properties, Solubility and Invitro drug release rate is increased with increase in PVP concentration from 0.25% to 1% as compared to sodium alginate.
Keywords: Nabumetone, agglomeration technique, solubility, dissolution rate, micromeritic properties.

INTRODUCTION

Much research has been conducted in to methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs[1]. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans, which may lead to therapeutic failure. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water[2-5]. Also formulation and manufacture of solid oral dosage forms and tablets in particular have undergone rapid changes and development over the last several decades. The basic requirement for commercial production of tablet is a particulate solid with good flowability, mechanical strength and compressibility[6]. Now a day's pharmaceutical industry prefers direct compression technique because of its economical facility in processing without the need of moisture and heat with less number of processing steps. In direct tabletting method, it is necessary to increase flowability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tabletting machine and sufficient mechanical strength of the compacted tablets[7]. In addition to increasing efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder[8]. Among the various methods, spherical crystallization is a versatile process that enables to control the type and size of the crystals. Spherical agglomeration is a size enlargement technique which is first developed by Kawashima in 1986 and he has defined spherical crystallization as a novel agglomeration technique by which both crystallization and agglomeration shall be carried out simultaneously in one step that can transform directly the fine crystals produced in the crystallization into a spherical form[9].The technique had been used to improve the powder micromeritic properties (flowability and compressibility) and dissolution of drug[10,11,12] . Then polymers were introduced in this system to modify their release[13, 14]. The various parameters were optimized in this such as type, amount and mode of addition of bridging liquid, temperature, agitation speed and reaction time to get more practical yield of spherical agglomerates. General methods of spherical crystallization are spherical agglomeration, emulsion solvent diffusion and ammonia diffusion method. The principle steps involved in the process of spherical crystallization are flocculation zone, zero growth zone, fast growth zone and constant size zone[15]. Nabumetone is widely used in the treatment of inflammation and pain associated with rheumatic disorders such as rheumatoid arthritis, osteoarthritis and also postoperative pains. It exhibits poor flow and compression characteristics and is hence a suitable candidate for spherical crystallization process to improve the flow properties and compressibility[16]. To reach the valuable goal of improving the therapeutic efficacy of water insoluble NSAID drug Nabumetone it is essential to improve the aqueous solubility of drug.

EXPERIMENTAL

Materials

Nabumetone was a gift sample from Devis Laboratories, Hyderabad, India. PVP K-30 &Sodium alginate were purchased from S.D. Fine Chemicals, India. All other chemicals used were of analytical reagent grade.

Process development and optimization

Spherical agglomerates of Nabumetone were prepared by the simple agglomeration technique using a three solvent system on basis of miscibility of solvent and solubility of drug involving good solvent (acetone), a poor solvent (water) and a bridging liquid (dichloromethane). Here agglomerates were

formulated using dichloromethane as bridging liquid which helps in binding of agglomerates by wetting the surface of agglomerates. The spherical agglomerates were formed by aggregation of these dispersed crystals. In this study we used the hydrophilic polymers like sodium alginate and PVP to provide strength and sphericity to the agglomerates. It was observed that PVP is more hydrophilic as compared to sodium alginate in improving micromeritic properties which ultimately increase the water solubility as well as in vitro release.

Designing the spherical crystallization process requires optimization of various process variables, which could affect the preparation and properties of the spherical crystals. The method of crystallization was optimized and validated according to the study of variables.

Method of preparation of agglomerates

In this study, solvent change method was used for the preparation of spherical crystals of Nabumetone. The drug Nabumetone (2gm) was dissolved in acetone (a good solvent) and hydrophilic polymers (PVP K-30 and Sodium alginate, 0.25–1%, *m*/*V*) in 100 ml distilled water. The drug solution was added to a polymeric solution which was maintained with continuous stirring at speed of 500± 25 RPM. The bridging liquid dichloromethane was added drop wise with mechanical stirring for 30 minutes. The spherical crystals were collected by filtration and dried at room temperature for 2hours .

Table - 1: Effect of variables on formulation of spherical agglomerates of Nabumetone[17]

S.NO	PARAMETERS	VARIABLES	OBSERVATION
1	Bridging liquids	Hexane	No agglomerates
		Toluene	lump formation
		Dichloromethane	Spherical agglomerates
		Benzene	No formation of agglomerates
		Chloroform	lump formation
2	Amount of bridging liquid (ml)	< 2.8	No agglomeration
		2.8	Spherical agglomerates
		> 2.8	Irregular shaped agglomerates
3	Agitation speed(rpm)	300	No agglomeration
		400	Spherical but large agglomerates
		500	Spherical agglomerates
		600	Irregular but small shaped agglomerates
		700	Irregular but small shaped agglomerates
4	Agitation time (min)	5	No Spherical agglomerates
		15	In complete agglomerates
		30	Spherical agglomerates

CHARACTERIZATION

IR, DSC & SEM Studies

The infrared (IR) spectra of powder Nabumetone, physical mixture and the agglomerates were recorded on an IR-spectrophotometer (FTIR 8300, Shimadzu, Japan) by the KBr pellet technique. Differential scanning calorimetry (DSC) analysis was performed using a DSC-60 calorimeter (Shimadzu).The surface morphology of the agglomerates was assessed by scanning electron microscopy (SEM) (Leica StereoScan 430, LEO, UK).

Micromeritic Properties

The loose bulk density (LBD) and tapped bulk density (TBD) of pure drug Nabumetone and its spherical crystals were determined using measuring cylinder method. Carr's index was calculated using LBD and TBD values [18] .The angle of repose was assessed by the fixed funnel method [19]. A known amount of agglomerates was allowed to flow through a funnel fixed at a constant height (*h*).The height (h) and diameter (2*r*) of the pile of powder were measured to calculate the angle of repose as $\tan \theta = h/r$.

Drug Loading Efficiency

The drug loading efficiency of crystals was determined by dissolving 100 mg of crystals in 100 ml of methanol, followed by measuring the absorbance of appropriately diluted solution spectrophotometrically (PharmaSpec UV-1700, UV-Visible Shimadzu) at 271 nm.

Solubility Studies

The solubility of nabumetone spherical agglomerates in water and 2% SLS was determined by taking excess quantity of spherical agglomerates and adding to screw-capped 50 ml of volumetric flask filled with water and 2% SLS. The volumetric flasks were shaken for 2 h on mechanical shaker. The solution was filtered through Whatmann filter paper No. 1 and the drug concentration was determined spectrophotometrically at 271 nm. Each sample was done in triplicate.

In vitro Dissolution Studies

The *in vitro* dissolution studies were carried out using 8 stations USP 23 dissolution testing apparatus (Electro lab, India). The dissolution medium used was 900 ml of 2%, *m*/*v* sodiumlaurylsulphate (SLS). The agglomerates containing 500 mg of Nabumetone were weighed and filled into a hard gelatin capsule. In the case of pure drug, 500 mg of pure Nabumetone was weighed and filled into a capsule. The capsule was then introduced into the dissolution medium. The medium was stirred at 75 rpm using a paddle at 37 ±0.5 °C. The samples were collected and analyzed spectrophotometrically.

Statistical analysis

The results were analyzed by two tailed Student's *t*-test using the Graph Pad Instat Software (GPIS; Version: 1.13)[20]. The mean dissolution time (*MDT*) was calculated using the Origin software.

RESULTS AND DISCUSSION

IR Studies

The interaction between the drug and the polymer was studied by IR spectroscopy and DSC. The IR peaks of pure drug Nabumetone, physical mixture and spherical agglomerates are shown in Fig 1 and Table1. IR spectra of Nabumetone showed characteristics peaks at 3062 cm^{-}

[1](aromatic C-H stretching),2956&2848 cm^{-1}, 2916 & 2812 cm^{-1} (C-H stretching of CH_3-O-CH_3 and CH_2 groups asymmetric and symmetric resp.) ,1705 cm^{-1} (C=O),1634,1608,1505&1485 cm^{-1} (C=C ring stretching),1452&1387cm^{-1}, 1410&1363cm^{-1} (C-H bending of CH_3,OCH_3,&CH_2 groups asymmetric and symmetric) , 1028cm^{-1} (C-O-C) ,957,895,845cm^{-1} (fused and substituted aryl rings).The comparison of IR spectra of pure drug, physical mixture of drug and polymer along with that of spherical agglomerates of Nabumetone (NA-P-4) reveals that there is no change in position of characteristic absorption bands. This suggests that the drug has not undergone interaction with polymer (sodium alginate, PVP K 30) and other excipients.

DSC Studies

DSC thermograms were shown in Fig 2 for pure drug Nabumetone and polymers PVP K30 & Sodium Alginate. The DSC study indicates that there is no appreciable change in the nature of thermo grams. The pure drug showed sharp endothermic peak with highest peak area at a melting point of 81.13^0c, which is in agreement with the literature M.P. The DSC thermogram of the formulation of spherical agglomerate of Nabumetone with PVP K30 and sodium alginate showed endothermic peaks with comparatively reduced areas at melting point of 79.82^0c and 79.68^0c. The lowering of m.p shows that change may be due to crystallization of drug with solvent acetone. As there is no much change in the thermal behavior of the drug and its formulations as indicated by the thermo grams, it can be concluded that the drug has retained its identity even in formulations and indicates there is no interaction between the drug and polymers used in the present study.

XRD Studies

X-ray powder diffractometry (XRPD) is a powerful technique for the identification of crystalline solid phases. Every crystalline solid phase has a unique XRPD pattern, which can form the basis for its identification. The X-ray powder diffraction pattern in the range 2Ɵ-50Ɵ showed in Fig 3, that the characteristic diffraction peaks of Nabumetone which were still detectable in the crystallized samples, suggesting that the particles get crystallized in the presence of sodium alginate and PVP-k-30 did not undergo any structural modifications. However, the differences in the relative intensities of their peaks are due to the differences in the crystallinity of particle size of the samples and decrease in the intensities may be due to change in sphericity. It is very difficult to identify the presence of sodium alginate or PVP-k-30 in XRPD spectra as they are polymers with amorphous structure and therefore no Sharp peaks are apparent at particular 2Ɵ due to the very low crystallinity of the components in the form of spherical agglomerates.

Scanning Electron Microscopy Studies

Physical characterization of agglomerates can be done by SEM analysis to assess typical shape of agglomerates and untreated drug. The spherical single agglomerate is formed by closely compacted fine rectangular shaped crystals which give evidence of enlargement of crystal surface of Nabumetone leading to increase flowability and compression property. The surface morphology of prepared agglomerates with 1% PVP and polymer is shown in figure 4. (36X) and figure 4 (160X) of D, E, F. and also spherical agglomerates of Nabumetone shown figure 4 figure 4 (100X, B) were spherical but no sphericity and smooth surface. The SEM analysis showed that the prepared agglomerates were spherical in shape with smooth and regular surface.

Micromeritic Properties

The results of loose bulk density (LBD) and tapped bulk density (TBD) are presented in Table - 2. These parameters were used to assess the packability of the crystals. The pure drug powder was more bulky and fluffy, which was indicated by the lowest LBD value (0.184± 0.00058 gmL-1,n=3).The highest TBD value (0.278± 0.001gmL-1,n=3)of pure drug indicates a high intergranular space between particles. In contrast, the spherical agglomerates exhibited higher LBD (0.231± 0.0015 to 0.253±0.0005 gmL-1,n=3) and TBD (0.247± 0.00057 to 0.277±0.00058gmL-1,n=3)values. These results indicate good packability of the prepared spherical crystals when compared with pure Nabumetone.

The results of Carr's index, Hausner's ratio and angle of repose of spherical crystals in comparison with pure drug are presented in Table - 2. These parameters were used to assess the flow and compressibility properties of the agglomerates. Carr's index and Hausner's ratio of pure drug were 33.57±0.0058% and 1.50 ±0.0058(n =3),respectively, indicating extremely poor flow properties. The powder could not pass through the funnel during the angle of repose experiment. The poor flow of Nabumetone could be due to the irregular shape and high fineness of the powder, which posed hurdles in the uniform flow from the funnel. On the other hand, all the prepared spherical agglomerates exhibited low Carr's index, Hausner's ratio and angle of repose values, indicating excellent flow properties and compressibility (Carr's index: 5.70 ±0.0153 to 9.88± 0.005%,n=3: Hausner's ratio:1.07± 0.01 to 1.11 ±0.005,n=3;angle of repose:23.02 ±0.27 to 27.09±0.0058o,n=3). Similarly the spherical agglomerates of Nabumetone prepared without polymer (SP) exhibited low Carr's index, Hausner's ratio and angle of repose values, indicating excellent flow properties and compressibility (carr's index:10.5 ±0.0058%,n=3; Hausner's ratio:1.11± 0.0058,n=3;angle of repose:28.49 ±0.015o,n=3). The improved flowability and compressibility of spherical agglomerates may be due to the sphericity, regular and larger size of crystals[]. Among all the prepared spherical crystals, the agglomerates prepared with 1%, *m*/*V*, PVP exhibited good micromeritic properties .

Table – 2: Micromeritic properties of agglomerates and pure drug[a]

Spherical crystals	LBD (g mL–1)	TBD (g mL–1)	Carr's index (%)	Hausner's ratio	Angle of repose (°)	Particle Size (µm)
NS1	0.253±0.001[b]	0.276 ±0.18[b]	8.33±0.01[b]	1.09±0.01[b]	25.64±0.13	199.52±0.12[b]
NS2	0.237±0.0015[b]	0.263±0.00058[b]	9.88±0.01[b]	1.11±0.005[b]	27.09±0.0058	218.77±0.11[b]
NS3	0.253 ±0.0005[b]	0.277±0.00058[b]	8.66±0.02[b]	1.09±0.005[b]	26.56±0.0099	239.88±0.10[b]
NS4	0.237 ± 0.0005[b]	0.263±0.001[b]	9.88±0.005[b]	1.11±0.005[b]	26.86±0.005	251.18±0.12[b]
NP1	0.241±0.0005[b]	0.258±0.00153[b]	6.59 ± 0.0058[b]	1.07±0.005[b]	24.75±0.01	208.12±0.13[b]
NP2	0.231 ±0.0015[b]	0.247±0.0005[b]	6.48±0.01[b]	1.07±0.01[b]	24.57±0.12	229.08±0.15[b]
NP3	0.231±0.001[b]	0.247±0.00057[b]	6.48±0.01528[b]	1.07±0.01[b]	23.62±0.02	257.03±0.11[b]
NP4	0.248±0.00152[b]	0.263± 0.001[b]	5.70±0.0153[b]	1.07±0.0152[b]	23.02±0.27	263.02±0.10[b]
DRUG	0.184±0.00058[b]	0.278±0.001	33.57±0.0058[b]	1.5±0.0058[b]	-----	87.09±0.12[b]
SP	0.247±0.00057[b]	0.276±0.00058[b]	10.5±0.0058[b]	1.11±0.0058[b]	28.49±0.015	131.82 ±0.22[b]

LBD – loose bulk density, TBD – tapped bulk density.
a Mean ± SEM, $n = 3$.
b Significantly different compared to pure Nabumetone ($p < 0.05$).

Drug loading and solubility studies

The results of drug loading efficiency and aqueous solubility are shown in Table - 3. The drug loading efficiency of spherical agglomerates is in the range 93.7 ± 2.3 to 98.6 ± 1.3 ($n = 3$), indicating negligible loss of drug during the crystallization process. The results of solubility studies indicate that pure Nabumetone possesses a very low solubility in water (2.43 ± 1.1 µg mL^{-1}, $n = 3$) while as in 2% SLS shows (438 ± 1.3 µg mL^{-1}, $n = 3$) because of its surfactant property. Solubility of spherical agglomerates without polymer showed (3.1 ± 1.2 µg mL^{-1}, $n = 3$) where as in 2% SLS showed (582.2 ± 1.1 µg mL^{-1}, $n = 3$). However the drug solubility from the Spherical Agglomerates increased significantly ($p < 0.05$), demonstrating that the incorporation of Sodium Alginate and PVP–K30 as polymers in different concentrations enhances the drug solubility in water as well as in 2% SLS from (5.37 ± 1.2; 617.8 ± 1.1 µg mL^{-1}, $n = 3$) to (7.64 ± 1.1; 831.1 ± 1.2 µg mL^{-1}, $n = 3$) by improving wettability. Maximum solubility from spherical agglomerates was observed at 1% (m/V) PVP-K30 (7.64 ± 1.1 µg mL^{-1}, $n = 3$). Similar results were observed with 2% (m/V) SLS (Table - 3).

Table - 3: Drug loading efficiency and Solubility data for the Agglomerates and Pure drug[a]

Spherical crystals	Drug loading (%)[b]	Solubility (µg mL^{-1})	
		Water (µ gm/ml)	SLS (2%, *m/V*)
NS1	98.2 ± 1.2	5.37± 1.2[c]	617.8± 1.1[c]
NS2	96.0 ± 1.3	5.42± 1.0[c]	631.1±1.5[c]
NS3	94.6 ± 1.3	5.73± 1.4[c]	648.9±1.3[c]
NS4	94.2 ± 1.2	5.82± 1.5[c]	657.8±1.1[c]
NP1	98.7 ± 1.3	7.33± 1.8[c]	804.4±1.5[c]
NP2	97.3 ± 1.1	7.46± 1.6[c]	813.3±0.5[c]
NP3	95.5 ± 1.2	7.51± 1.3[c]	823.2± 1.3[c]
NP4	93.7 ± 2.3	7.64± 1.1[c]	831.1±1.2[c]
DRUG	100 ± 0.0	2.43±1.1	438.2±1.3
SP	93.3 ± 1.3	3.1±1.2[c]	582.2±1.1[c]

a Mean ± SEM, $n = 3$.
b Drug loading is expressed as % or mg of drug per 100 mg of crystals.
c Significantly different compared to pure Nabumetone ($p < 0.05$).

In –Vitro Evaluation

The results of *in vitro* dissolution studies are shown in Fig. 5 and Table 5. Pure drug Nabumetone exhibited less release at the end of 180 min in 2% SLS (69.88 ± 0.2%, $n = 3$) with MDT 14.47±0.30 min, n=3. Dissolution rate of Nabumetone Spherical agglomerates in 2%SLS was (71.581 ± 0.2%, $n = 3$) with MDT (13.68±0.30 min, n=3). Spherical agglomerates showed increased dissolution rate in 2% SLS with increase in sodium alginate and PVP concentration in range of (76.966 ± 0.2, n=3) to (96.44 ± 0.2, $n = 3$) with MDT (14.22 ± 0.30 min, n=3) to (13.16± 0.30 min, n=3); but the mean dissolution time (MDT) of spherical agglomerates containing 1.0% PVP was low when compared to that of pure drug in 2% SLS (11.10± 0.30 min, n=3). This could be due to

increased wettability of the drug by the presence of PVP. This might be due to the surfactant property of SLS on the drug which shows maximum dissolution of drug within 120 min. The mechanism behind the solubility and dissolution rate enhancing effect of Nabumetone in crystal form may resemble the solid dispersion mechanism despite the large particle size of the crystals. This effect may be due to improved wettability of the surface of crystals by the adsorption of PVP onto the surfaces of crystals [21]. They also demonstrate that PVP is a suitable polymer for the preparation of spherical agglomerates of Nabumetone.

Table 4. Drug release and MDT[a]

Spherical Agglomerates	SLS (2%, *m*/*V*)	
	Nabumetone Released (%)	MDT (min)
NS1	100.0 ± 0.0 (after 3h)	16.58 ± 0.21[b]
NS2	100.0 ± 0.0 (after 3h)	15.81 ± 0.11[b]
NS3	100.0 ± 0.0 (after 3h)	14.22 ± 0.35[b]
NS4	100.0 ± 0.0 (after 3h)	13.13 ± 0.10[b]
NP1	100.0 ± 0.0 (after 3h)	13.91 ± 0.11[b]
NP2	100.0 ± 0.0 (after 3h)	13.44 ± 0.30[b]
NP3	100.0 ± 0.0 (after 3h)	13.16 ± 0.31[b]
NP4	100.0 ± 0.0 (after 2h)	11.10 ± 0.16[b]
DRUG	100.0 ± 0.0 (after 3h)	14.47 ± 0.29[b]
SP	100.0 ± 0.0 (after 3h)	13.68 ± 0.11[b]

MDT – mean dissolution time.

a Mean ± SEM, $n = 3$.

b Significantly different compared to pure Nabumetone ($p < 0.05$).

CONCLUSION

The present study shows that spherical agglomerates of Nabumetone prepared with PVP exhibited improved micromeritic properties which are essential requirement for direct tableting. Hence in addition to improving the solubility enhanced dissolution rate was observed compared to pure drug Nabumetone. So this technique may be applied for producing oral solid dosage forms of Nabumetone with improved dissolution rate and oral bioavailability.

REFERENCES

1)Mudit dixit, Parthasarathi Kulkarni, Vangala Gowtham, H G Shivkumar, Preparation and characterization of spray dried microparticle and chilled spray dried particle of ketoprofen by spray drying method Asian Journal of Pharmaceutical and Clinical Research 2011;4(1):138-142.

2) Corrigan DO, Corrigan OI and Healy AM Predicting the physical state of spray dried composites: salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol co-spray dried systems. Int. J. Pharm.2004; 273: 171-182.

3) Craig DQM The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm. 2002; 231: 131-144.

4) Kamble R, Maheshwari M, Paradkar AR and Kadam S .Melt solidification technique: Incorporation of higher wax content in ibuprofen beads. AAPS PharmSciTech. 2004; 5(4): Article 6.

5) Kapsi SG , Ayres JW. Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution and bioavailability. Int. J. Pharm. 2001; 229:193-203.

6) M.M.Gupta**,** B. Srivastava, Monika Sharma, Vinita Arya. **S**pherical crystallization: a tool of particle engineering for making drug powder suitable for direct compression. International Journal of Pharma Research and Development.2010; 12(1):1-10.

7) Shangraw, R.F, Compressed Tablets by Direct Compression. In pharmaceutical Dosage Form: Tablets, Lieberman, H.A., L. Lachman and J.B. Schwartz (Eds). Marcel Dekker, New York Vol. 1, 1989; 195-246.

8) Gharaei-Fathabad, E., Biosurfactants in pharmaceutical industry: A mini-review. AM. J. Drug Discovery Dev 2011; 1: 58-69.

9) Kawashima Y., Okumura M. and Takenaka H. Spherical crystallization: direct spherical agglomeration of salicylic acid crystals during crystallization. Science, 1982; 216: 1127-1128.

10) Kawashima, Y. Development of spherical crystallization technique and its application to pharmaceutical system. Arch. Pharm. Res 1984; 7: 145-151.

11) Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K. Improvements in flowability and compressibility of pharmaceutical crystals for direct tabletting by spherical crystallization with a two solvent system, Powder Technology 1994; 78: 151-157.

12) Bodmeier R, Paeratakul R. Spherical agglomerates of water-insoluble drugs, J Pharm Sci 1989; 78: 964-967.

13) Di Martino P, Barthelemy C, Piva F, Joiris E, Palmieri GF, Martelli S. Improved dissolution behavior of fenbufen by spherical crystallization, Drug Dev Ind Pharm 1999; 25: 1073-1081.

14) Sano A, Kuriki T, Kawashima Y, Takeuchi H, Hino T, Niwa T. Particle design of tolbutamide by spherical crystallization technique. IV, Improvement of dissolution and bioavailability of direct compression tablets prepared using tolbutamide agglomerated crystals,Chem .Pharm.Bull 1992; 40: 3030-3035.

15) Yadav A.V, Designing of pharmaceuticals to improve physicochemical properties by spherical crystallization technique, Journal of Pharmacy Research. Oct-December 2008; 1(2): 105-112.

16) Kulkarni P.K; Subash Chandra Bose .P, Spherical Agglomerates of Nabumetone, Indian Journal of Pharmceutical Education and Research Jan-mar 2007; 41 (1):18.

17) Chorasia M. K. Preparation and characterisation of agglomerated spherical crystals of ibuprofen. Indian Journal of Pharmaceutical Science, 2007; 364-368.

18) J. Wells, Pharmaceutical preformulation, the physicochemical properties of drug substances, in Pharmaceutics the Science of Dosage Form Design, 2nd ed. (Ed. M. E. Aulton), Churchill Living stone, London 2002; 113–138.

19) A. Martin, P. Bustamante and A. Chun, Micromeritics, in Physical Pharmacy – Physical Chemical Principles in the Pharmaceutical Sciences, 4th ed., Lippincott Williams and Wilkins, Baltimore 2002; 423–452.

20) S. Mutalik and N. Udupa, Pharmacological evaluation of membrane moderated transdermal system of glipizide, Clin. Exp. Pharmacol. Physiol. 1–2, 2006; 17–26.

21) S. Kawashima, T. Handa, H. Takenchi, M. Okumura, H. Katou and O. Nagai, Crystal modification of phenytoin with polyethylene glycol for improving mechanical strength, dissolution rate and bio-availability by a spherical crystallization technique, Chem. Pharm. Bull. 1986; 34: 3376–3383.

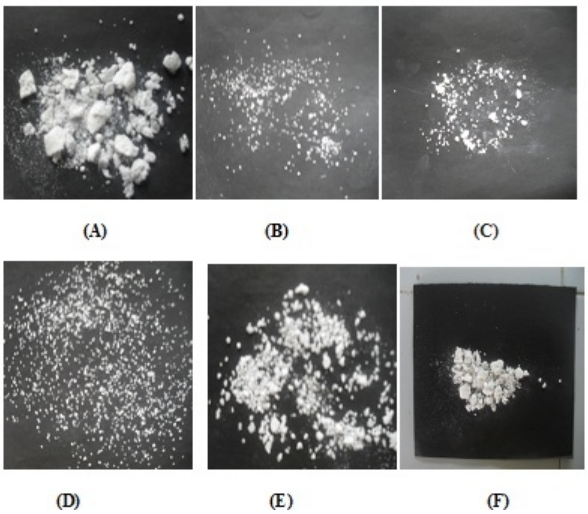

Fig – 1: Photographs showing effect of process variables on Agglomeration (A) Lump formation (B) Spherical agglomerates (C) Irregular shaped agglomerates (D) Spherical agglomerates (E)Spherical but large agglomerates (F) In complete agglomerates

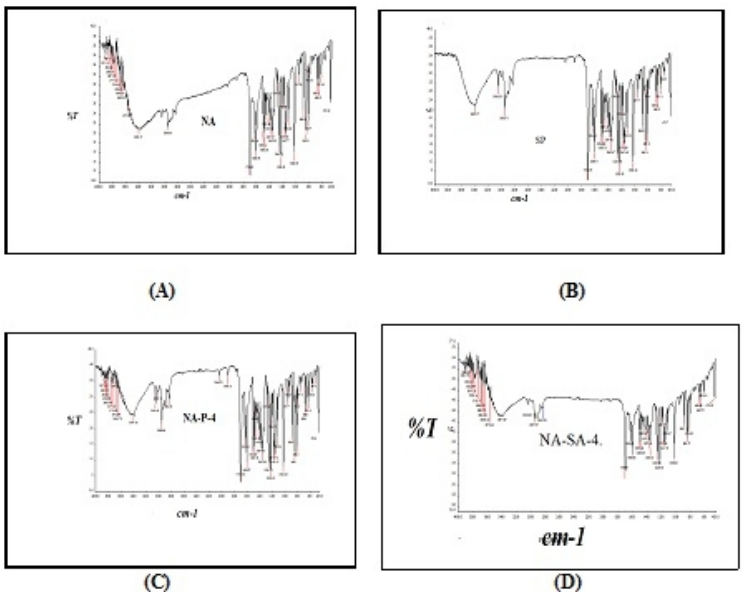

Fig – 2: IR Spectra of (A) Pure drug Nabumetone; (B) Spherical agglomerate of Nabumetone; (C) Nabumetone Spherical agglomerate with PVP polymer; (D) Nabumetone Spherical agglomerate with Sodium alginate polymer.

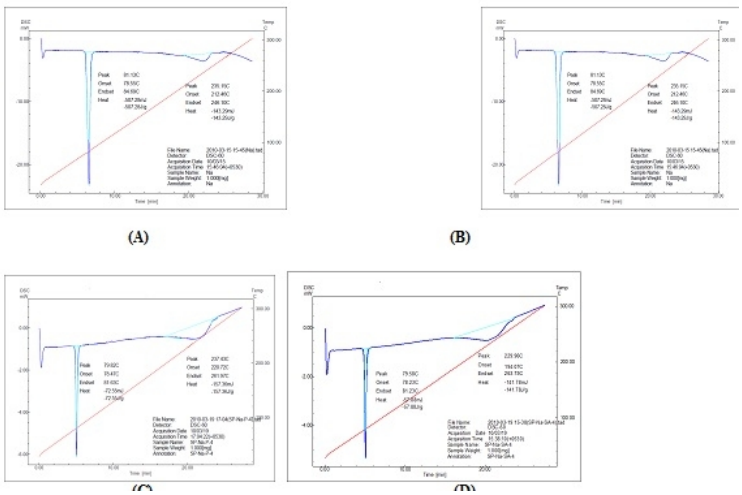

Fig – 3: DSC Thermograms of (A) Nabumetone, Pure drug (B) spherical agglomerates of Nabumetone, (C) Nabumetone Spherical agglomerates with PVP polymer (D) Nabumetone Spherical agglomerates with sodium alginate polymer

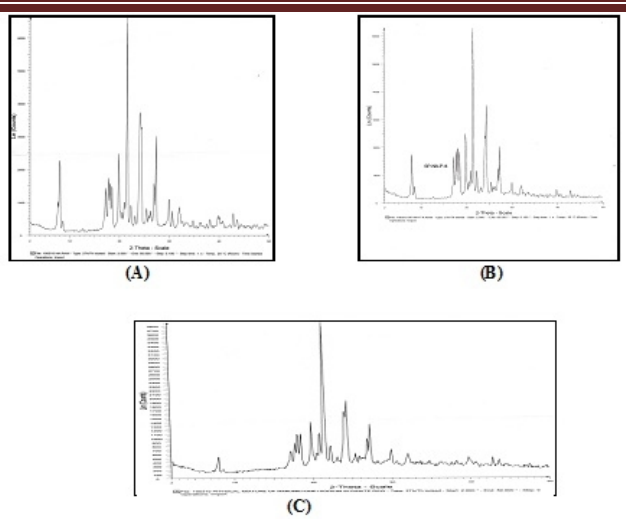

Fig – 4: XRD analysis of (A) Pure drug Nabumetone; (B) PVP K-30 Spherical agglomerates of Nabumetone; (C) Sodium alginate spherical agglomerates of Nabumetone

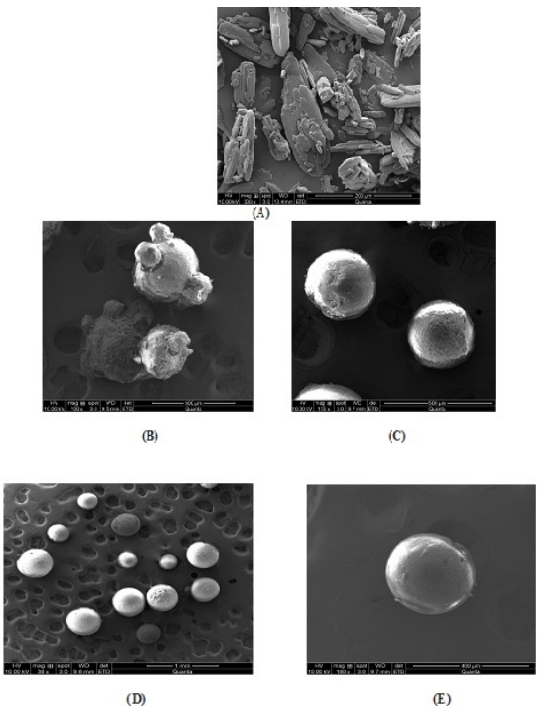

Fig – 5: SEM analysis of A) Nabumetone pure drug; B)Spherical agglomerate of Nabumetone of 100X magnification; (C,D,E,) Spherical agglomerate of Nabumetone with polymer 1% PVP k-30 with magnification 135x, 36x,160x

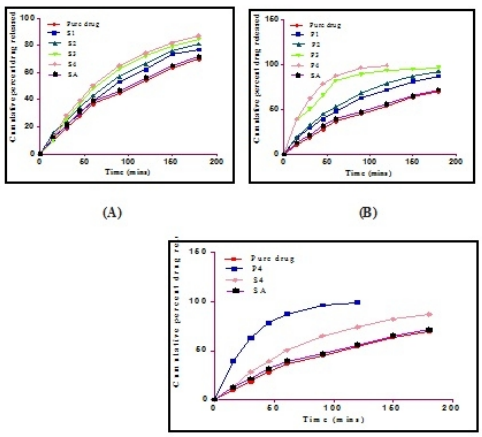

Fig – 5: Cumulative Percent Drug Release of **(A)** Sodium Alginate Nabumetone Spherical Agglomerates in different concentrations with pure drug and Plain agglomerates; **(B)** PVP Nabumetone spherical agglomerates in different concentrations with pure drug and Plain agglomerates; **(C)** 1% PVP and sodium alginate Nabumetone spherical agglomerates' with pure drug and Plain agglomerates

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