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Formulation Of Crystallo-Co-Agglomerates Of Naproxen: Study Of Effect Of Polymers On Drug Release

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Abstract: The aim of the present work was to develop spherical agglomerates of naproxen by crystallo-co-agglomeration technique. Acetone-chloroform-water system containing PVP K30, PEG 4000 and Sodium carboxymethylcellulose was used as the crystallization medium. Acetone acted as a good solvent for naproxen, chloroform as bridging liquid and aqueous phase as non-solvent. The compatibility study was done by DSC, FTIR and surface morphology was done by SEM. The growth of particle size and the spherical form of the agglomerates resulted in formation of products with good flow and packing properties. Drug release studies were performed in phosphate buffer pH 7.4 for 25 min. The dissolution data demonstrated that the rate of drug release is dependent upon the nature and concentration of polymer used in the formulation. FTIR and DSC studies showed that naproxen particles, crystallized in the presence of PVP K30, PEG 4000 and Sodium CMC did not undergo structural modifications. Formulation, PP2 containing combination of polymers (PVP K30 and PEG 4000) in the ratio 1:0.75 was selected as an optimized formulation which showed better results with respect to percent drug release, percent yield, MDT and % DE when compared to other formulations.
Key words: Naproxen, Spherical agglomerates, Crystallo-co-agglomeration, PVP K30, Sodium carboxy methylcellulose, PEG 4000.

Introduction:

Recently there have been greater advancements in powder technology and different attempts are made to design primary and secondary particles of pharmaceutical substances for several applications. Enlargement of particle size is an important process in manufacturing of tablets and is used to impart some degree of functionality to particles such as improvement in flowability, micromeritic, compression and compactability properties. Different techniques for enlargement of particle size are important tools in modifying primary and secondary properties of pharmaceutical substances. Now-a-days several new techniques combining granulation and crystallization are being developed to improve particle properties. There are various conventional process which are used to enlarge the particle size and involves wider acceptability but recently different non-conventional techniques of particle size enlargement are being developed which include extrusion-spheronisation, melt solidification, melt granulation, melt extrusion and spherical agglomeration.[1] These techniques are advantageous due to less number of unit operations and economic in terms of processing cost and depend on the desired properties of the enlarged particle and the physicochemical properties of the drug and excipients.[1]

Spherical agglomeration can be defined as “a novel particle engineering technique by which agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted

spherical form".[2,3] Besides producing spherical crystals it also enables co-precipitation of drugs and encapsulating polymers in the form of spherical particles. This technique can also be exploited to increase solubility, dissolution and hence bioavailability of poorly soluble drugs.[4,5]

The two most commonly used techniques of spherical agglomeration are wet spherical agglomeration method (WSA), quasi-emulsion solvent diffusion method (QESD, Transient emulsion).[6,7] But there are two extensions of these techniques, ammonia diffusion system (ADS) and crystal-co-agglomeration technique (CCA).[8,9] Another technique of this process is Neutralization, where first fine crystals form by neutralization then it will agglomerate with the help of a bridging liquid.[10]

CCA is a novel technique developed by Kadam *et al.* to overcome the limitations of spherical crystallization.[11] It is a modification of the spherical crystallization technique and used for size enlargement of all, low dose, high dose, poorly compressible drugs and combination of drugs with or without diluents. In this technique drug is directly crystallized and agglomerated in combination with an excipient or with another drug with help of bridging liquid. Excipient or drug may or may not be crystallized in this system[12]. An excipient which is used in this technique should have affinity toward the bridging liquid.

In the present study, the agglomeration of naproxen was carried out in the presence of hydrophilic polymers such as PVP K30, PEG 4000 and sodium carboxymethylcellulose. The aim of this study was to investigate the micromeritic and dissolution properties of naproxen agglomerated in the presence of above mentioned polymers.

Materials:

Naproxen was obtained as a gift sample from DIVI'S laboratories Ltd, Hyderabad, India. PEG 4000, Sodium carboxymethylcellulose (200-300 cps) and Chloroform was procured from SD fine chemicals, Mumbai, India. PVP K30 and Acetone was procured from HIMEDIA Laboratories Pvt. Ltd., Mumbai, India. All other chemicals and reagents used were of analytical grade.

Experimental:

Standard plot of Naproxen

The stock solution of naproxen was prepared and suitably diluted with phosphate buffer pH 7.4 to get 5, 10, 15, 20, 25 and 30 µg/ml concentration solutions and absorbance was recorded at 271 nm by UV-visible spectrophotometer (UV-1601, Shimadzu, Japan). Each study was conducted in triplicate.

Preparation of crystallo-co-agglomerates

A. Preparation of naproxen agglomerates by using PVP K30:

Naproxen agglomerates were prepared using a three solvent system comprising acetone: chloroform: water (good solvent, bridging liquid and bad solvent, respectively). In a vessel, PVP K30 was dissolved in sufficient amount of distilled water. Naproxen was dissolved in acetone maintained at 50^{o}C. The latter dispersion was added immediately to the dispersion containing dissolved polymer under constant stirring conditions (600 rpm) kept at room temperature. The stirring was continued for 20 min and bridging liquid chloroform was added drop wise to obtain agglomerates, which were then filtered and dried overnight. Three batches were prepared by changing the concentration of PVP K30 (0.5, 1 and 1.5 % w/v). The formulation, P1 containing 0.5 % w/v of PVP K30 yields a maximum of 95.04 % and hence it was selected as basic polymer with same concentration for further formulations.

B. Preparation of naproxen agglomerates by using PVP K30 and PEG 4000:

Naproxen agglomerates were prepared using a three solvent system comprising acetone: chloroform: water (good solvent, bridging liquid and bad solvent, respectively). In a vessel, PVP K30 (0.5% w/v) was dissolved in sufficient amount of distilled water and 1/3 of the total PEG 4000 was uniformly dispersed in the solution. Naproxen was dissolved in acetone maintained at 50^{o}C and the other 2/3 of PEG 4000 was also dissolved in it. The latter dispersion was added immediately to the dispersion containing dissolved polymer under constant stirring conditions (600 rpm) kept at room temperature. The stirring was continued for 20 min and bridging liquid chloroform was added drop wise to obtain agglomerates, which were then filtered and dried overnight. Three batches were prepared by changing the concentration of PEG 4000.

C. Preparation of naproxen agglomerates by using PVP K30 and sodium CMC:

Naproxen agglomerates were prepared using a three solvent system comprising acetone: chloroform: water (good solvent, bridging liquid and bad solvent, respectively). In a vessel, PVP K30 (0.5% w/v) was dissolved in sufficient amount of distilled water and sodium carboxymethylcellulose was uniformly dispersed in the solution. Naproxen was dissolved in acetone maintained at 50^{o}C. The latter dispersion was added immediately to the dispersion containing dissolved polymer under constant stirring conditions (600 rpm) kept at room temperature. The stirring was continued for 20 min and bridging liquid chloroform was added drop wise to obtain agglomerates, which were then filtered and dried overnight. Three batches were prepared by changing the concentration of sodium carboxymethylcellulose.

The composition of naproxen-polymer agglomerates are shown in table 1.

Table 1: Composition of naproxen-polymer agglomerates

Formulation	P1	P2	P3	PP1	PP2	PP3	PS1	PS2	PS3
Naproxen	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PVP K30	0.375	0.750	1.125	0.375	0.375	0.375	0.375	0.375	0.375
PEG 4000	-	-	-	0.187	0.281	0.375	-	-	-
Sodium CMC	-	-	-	-	-	-	0.187	0.281	0.375

Quantities of all ingredients are mentioned in gram units.

Evaluation of prepared agglomerates:

Solubility studies:

To evaluate the increase in the solubility of naproxen and its agglomerates solubility measurements were conducted. Excess amount drug or agglomerates was added to 50 ml volumetric flask containing distilled water. The system was agitated on a rotary shaker for 48 h at 100 rpm maintained at room temperature and filtered. The filtrate was suitably diluted and analyzed at 271 nm by using UV visible spectrophotometer (UV-1601, Shimadzu, Japan).

Micromeritic parameters:

A. Bulk density (D_b):

Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/ml and is given by,

$$D_b = M/V_o$$

Where, D_b = Bulk density (gm/ml)

M = mass of powder (g)

V_o = bulk volume of powder (ml)

B. Tapped density (D_t):

Accurately weighed sample of 10 gm was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/ml and is given by,

$$D_t = M/V_t$$

Where, D_t = Tapped density (gm/ml)

M = mass of powder (g)

V_t = tapped volume of powder (ml)

C. Compressibility index (CI):

The compressibility of the powder was determined by the Carr's compressibility index.

$$CI(\%) = \left[\frac{(D_t - D_b)}{D_t}\right] \times 100$$

D. Hausner ratio:

Hausner ratio is used for predicting powder flow characteristics.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

E. Angle of repose (θ):

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel until the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$$\theta = tan^{-1}\left(h/r\right)$$

Where,

θ = angle of repose

h = height of pile,

r = radius of the base of the pile.

Drug content:

An accurately weighed quantity of agglomerates equivalent to 100 mg of naproxen was taken in a 100 ml volumetric flask. The drug was then extracted by using phosphate buffer pH 7.4 by subjecting to continuous shaking on a rotary shaker for 4 h. Naproxen in the extracted fluid was analysed at 271 nm by using UV-visible spectrophotometer (UV-1601, Shimadzu, Japan) against phosphate buffer pH 7.4 solution as blank.

***In vitro* drug release studies:**

The *in vitro* drug dissolution study was performed using eight station dissolution test apparatus (Dissolution tester (USP) TDT-08L, Electrolab, India) with a paddle speed of 50 rpm. Dissolution medium consisted of 900 ml of phosphate buffer pH 7.4 maintained at 37 ± 0.5º C. At a predetermined time intervals an aliquot was withdrawn and replenished with fresh medium. Amount of drug in each aliquot was assayed on a UV-Spectrophotometer (UV-1601, Shimadzu, Japan) at 271 nm using phosphate buffer pH 7.4 as blank. All the trials were conducted in duplicate and the average (± S.D) reading was noted.

Model independent kinetics:

A. Dissolution efficiency:

Dissolution efficiency is used to translate the profile difference into a single value. Dissolution efficiency was calculated by using following equation.

$$DE\,\% = \frac{\int_0^t y\,dt}{y_{100}t} \times 100$$

Where, y is the drug percent dissolved at time t.

B. Mean dissolution time:

Mean dissolution time represents the mean time for drug molecules to completely dissolve. It is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of the polymer. MDT was calculated by using the following equation.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Where *'i'* is the dissolution sample number, *'n'* is the number of dissolution sample time, *'tmid'* is the time at the midpoint between *'i'* and *'i-1'*, and *'ΔM'* is the amount of drug dissolved between *'i'* and *'i-1'*.

FT-IR Spectrophotometric analysis:

The samples of drug, polymer and their mixture were prepared in the form of KBr pellets and subjected for scanning from 4000 cm^{-1} to 400 cm^{-1} using FT-IR spectrophotometer (FT-IR-8400, Shimadzu, Japan).

Differential scanning calorimetric analysis:

The samples were scanned from 0-400°C with the scanning rate of 10°C rise/min using differential scanning calorimeter (DSC-60, Shimadzu, Japan).

X-ray diffraction of powder (XRDP):

The X-ray powder diffraction patterns were recorded on an X-ray diffractometer (PW 1729, Philips, Netherland). The samples were irradiated with monochromatized CuK-α radiation (1.542A°) and analysed between 10-60° 2θ. The voltage and current used were 30kV and 30mA

respectively. The range and the chart speed were $1x10^4$ CPS and 5mm/2θ respectively.

Scanning Electron microscopy:

The shape and surface topography of pure naproxen and drug-polymer agglomerates were observed through a scanning electron microscope (Joel- LV-5600, USA).

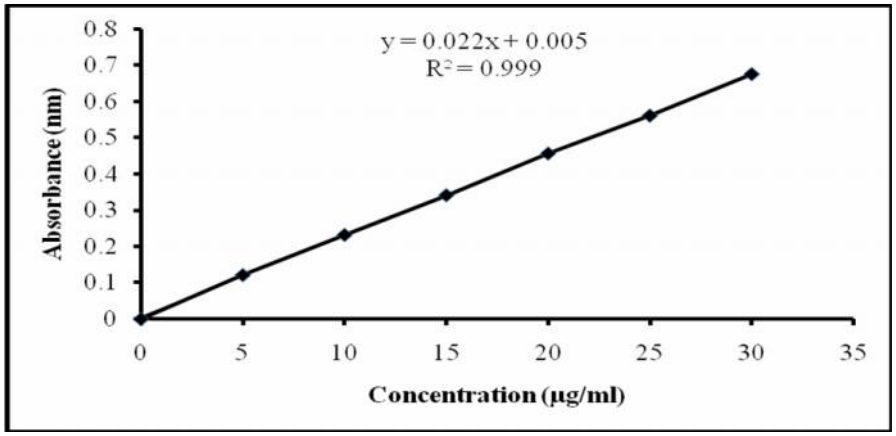

Figure 1: Calibration curve of naproxen in phosphate buffer pH 7.4

Results And Discussion

Calibration curve of Naproxen:

The calibration curve of Naproxen was developed in the range of 5-30µg/ml at wavelength 271nm. Good linearity with regression coefficient of 0.999 (r^2 value) was observed. The tested concentration range obeyed Beer's law (Figure 1).

Formulation development:

Naproxen was crystallized from acetone-chloroform-water and agglomerated with hydrophilic polymers such as PVP K30, PEG 4000 and sodium CMC. Naproxen is freely soluble in acetone (good solvent), but practically insoluble in water (anti-solvent). Also it is soluble in chloroform (bridging liquid) which is immiscible with

water. Hence, this solvent system was selected for the present study. In this process, crystallization of drug was performed by the addition of drug solution to the anti-solvent phase (water). The acetone solution (maintained at 50°C) containing drug was added immediately to the aqueous dispersion containing hydrophilic polymers viz. PVP K30, PEG 4000, sodium CMC or their combinations and quasi-emulsified droplets of drug solution were produced. The addition of bridging liquid (chloroform) promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by coalescence of these dispersed crystals. The effect of different variables on formulation of spherical agglomerates of naproxen are given in the table 9.

Solubility studies:

The results for solubility studies of pure Naproxen and drug-polymer agglomerates were shown in table no. 2. The solubility of Naproxen in distilled water was found to be 0.07±0.01 mg/ml. The solubility of Naproxen from agglomerates prepared were in the range of 0.14±0.02 mg/ml to 0.58±0.003 mg/ml. All the drug-polymer agglomerates showed an increase in drug solubility over NPX, PS3 showing the highest solubility of 0.58±0.003 mg/ml.

Micromeritic properties:

The results for micromeretic properties of pure Naproxen and drug agglomerates were shown in Table 3.

From the results of micromeritic studies it can be concluded that the agglomerates showed improvement in flow property when compared to pure Naproxen. Among different agglomerates prepared, formulation PS1 showed maximum flowability as evident by low values of angle of repose (31.2 ± 0.89^0), Hausner's ratio (1.14±0.09) and Carr's index (12.35±0.08 %).

Table 2: Solubility studies of pure naproxen and drug-polymer agglomerates.

Formulation	Solubility (mg/ml)
NPX	0.07±0.01
P1	0.14±0.02
P2	0.147±0.004
P3	0.153±0.03
PP1	0.162±0.002
PP2	0.171±0.003
PP3	0.179±0.004
PS1	0.41±0.040
PS2	0.47±0.002
PS3	0.58±0.003

Values are mean ±SD, n=3

Table 3: Micromeritics of pure naproxen and drug-polymer agglomerates.

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner ratio	Angle of repose (ɵ)
NPX	0.331±0.02	0.488±0.03	32.17±0.04	1.47±0.05	57.8±0.90
P1	0.384±0.04	0.496±0.08	22.58±0.06	1.29±0.07	42.9±1.10
P2	0.393±0.04	0.499±0.04	21.32±0.05	1.21±0.04	41.3±0.83
P3	0.389±0.03	0.494±0.12	22.25±0.02	1.26±0.03	42.2±0.67
PP1	0.401±0.05	0.498±0.09	19.49±0.07	1.23±0.08	39.6±1.16
PP2	0.404±0.03	0.509±0.06	20.62±0.04	1.25±0.05	36.4±1.19
PP3	0.412±0.06	0.503±0.03	18.09±0.05	1.22±0.04	37.7±0.94
PS1	0.454±0.12	0.518±0.02	12.35±0.08	1.14±0.09	31.2±0.89
PS2	0.441±0.08	0.514±0.10	14.20±0.09	1.16±0.08	33.8±1.20
PS3	0.442±0.09	0.524±0.05	15.64±0.07	1.18±0.08	34.5±0.79

Values are mean±SD, n=3

Table 4: Drug content (%) and % yield of naproxen-polymer agglomerates.

Formulation	P1	P2	P3	PP1	PP2	PP3	PS1	PS2	PS3
Drug content (%)	98.5± 0.66	99.1± 1.23	99.5± 0.25	100± 0.54	101.8± 0.96	101.1± 1.26	99.8± 1.3	99.2± 0.45	100.3± 0.37
% yield	95.04 ±0.92	63.33 ±1.32	55.77 ±1.27	84.63± 0.59	85.02± 0.46	66.41± 1.25	67.07± 0.76	62.61± 0.46	61.33± 0.26

Values are mean±SD, n=3

Drug content and % yield

The percentage drug content of all the formulations (agglomerates) in phosphate buffer pH 7.4 varied from 98.5±0.66 to 101.8±0.96 as shown in Table 4. This showed that there was uniform distribution of drug throughout the batch**.**

The % yield of agglomerates prepared was in the range of 55.77±1.27 to 95.04±0.92 %.

***In vitro* dissolution studies**

Dissolution behavior of pure Naproxen and agglomerates was studied using phosphate buffer pH 7.4 as dissolution medium (**table 5-7 and figure 2-4). The** amount of pure Naproxen dissolved in phosphate buffer pH 7.4 was 59.96±0.46 % at 25 min.

Among the agglomerates prepared by using PVP K30 alone, formulation P3 containing 1.5 % w/v of PVP K30 showed maximum drug release of 98.39±0.72 % at 25 min and from the agglomerates prepared by using combination of PVP K30 and PEG 4000, formulation PP3 containing both the polymers in 1:1 ratio showed maximum drug release of 104.57±0.25 % at 25 min.

From the dissolution behavior of agglomerates prepared by using single polymer (PVP K30) and by combination of polymers (PVP K30, PEG 4000) it is found that the percent drug release from agglomerates increased as the amount of polymer added was increased.

In case of agglomerates prepared by using combination of PVP K30 and Sodium CMC, the percentage drug release decreases as the amount of Sodium CMC is increased. This may be due to the binding effect of Sodium CMC as its concentration is increased. Formulation PS1 containing least polymer ratio of 1:0.5 (PVP K30: Sodium CMC) showed drug release of 66.46±0.94 % at 25 min whereas the formulation PS3 containing high polymer ratio of 1:1 (PVP K30: Sodium CMC) showed drug release of 61.97±0.47 % at 25 min.

Table 5: Comparison of *in vitro* dissolution profile data of naproxen in pure form and P1, P2 & P3.

Time(min)	Cumulative % Drug Released			
	NPX	P1	P2	P3
0	0	0	0	0
5	17.86±1.17	73.49±0.94	75.40±0.47	77.99±0.23
10	31.04±0.47	80.99±1.47	84.28±0.71	87.01±2.36
15	44.17±0.46	87.44±0.95	90.33±0.94	95.00±0.72
25	59.96±0.46	93.51±0.49	95.87±0.71	98.39±0.72

Values are mean ± SD, n = 3

Table 6: Comparison of *in vitro* dissolution profile data of naproxen in pure form and PP1, PP2 & PP3.

Time(min)	Cumulative % Drug Released			
	NPX	PP1	PP2	PP3
0	0	0	0	0
5	17.86±1.17	80.86±0.46	90.13±0.23	92.58±0.47
10	31.04±0.47	93.03±0.47	96.22±0.71	98±1.18
15	44.17±0.46	97.5±0.70	100.98±0.24	102.91±0.71
25	59.96±0.46	101.17±0.23	102.9±0.22	104.57±0.25

Values are mean ± SD, n = 3

Table 7: Comparison of *in vitro* dissolution profile data of naproxen in pure form and PS1, PS2 & PS3.

Time(min)	Cumulative % Drug Released			
	NPX	PS1	PS2	PS3
0	0	0	0	0
5	17.86±1.17	49.22±0.23	47.99±0.47	45.54±0.46
10	31.04±0.47	58.77±0.71	55.35±0.23	50.43±0.46
15	44.17±0.46	61.82±0.46	59.34±0.46	53.43±0.23
25	59.96±0.46	63.93±0.71	62.94±0.23	60.82±0.23

Values are mean ± SD, n = 3

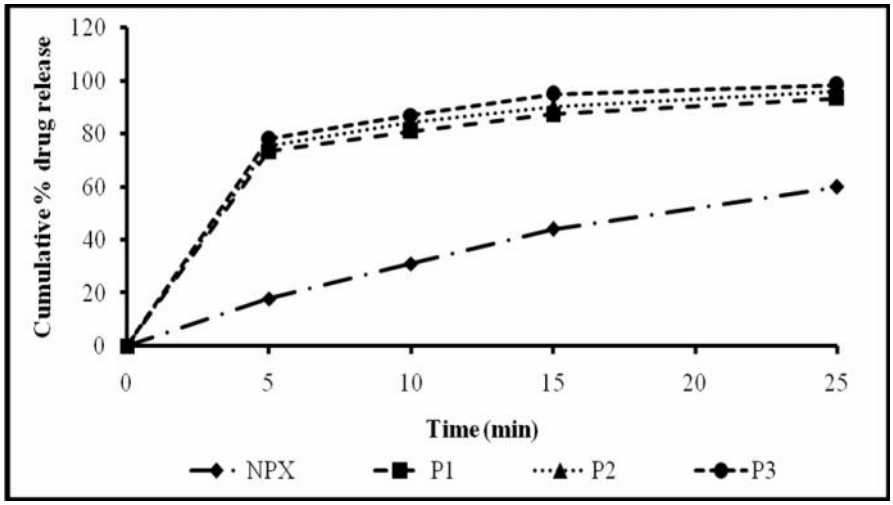

Figure 2: Comparison of *in vitro* dissolution profile data of naproxen in pure form and P1, P2 & P3.

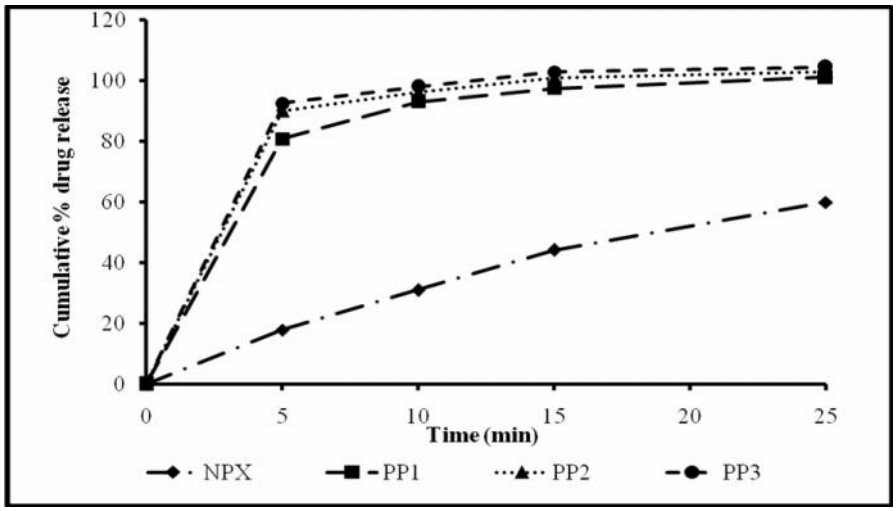

Figure 3: Comparison of *in vitro* dissolution profile data of naproxen in pure form and PP1, PP2 & PP3.

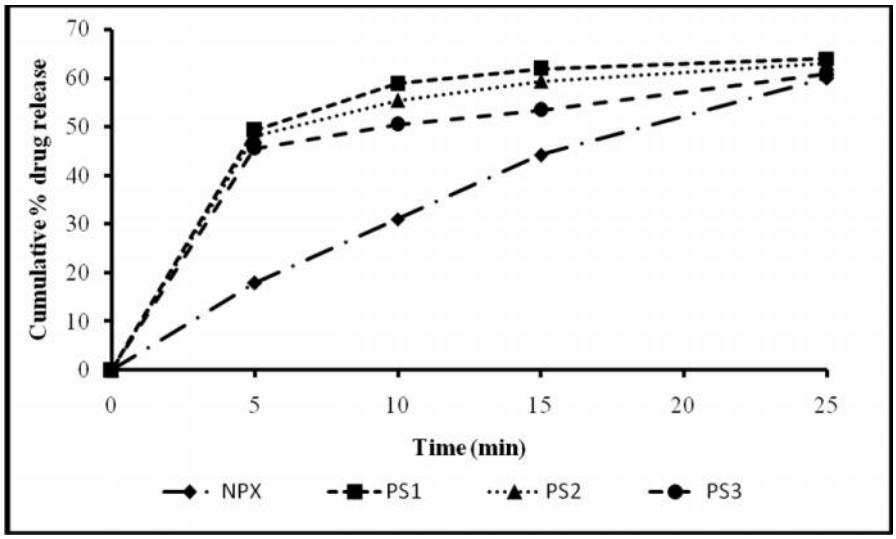

Figure 4: Comparison of *in vitro* dissolution profile data of naproxen in pure form and PS1, PS2 & PS3.

Table 8: Model Independent Kinetics

Formulation	MDT (min)	% $DE_{25\ min}$
P1	4.72	81.09
P2	4.60	79.29
P3	4.37	77.52
PP1	4.16	83.33
PP2	3.58	85.65
PP3	3.50	87.07
PS1	4.30	82.79
PS2	4.71	81.12
PS3	5.52	77.91

Table 9: Effect of variables on formulation of spherical agglomerates of Naproxen

Parameter	Variable	Observation
Concentration of bridging liquid (chloroform)	3.5%	No agglomeration
	5.5%	Agglomeration
	7%	Agglomeration (low % yield)
	10%	Agglomeration (low % yield)
Agitation speed	200±5 rpm	No agglomeration
	400±5 rpm	Incomplete agglomerates
	600±5 rpm	Spherical agglomerates
	800±5 rpm	Spherical and small
Agitation time	10 min	Incomplete agglomerates
	20 min	Spherical agglomerates
Temperature (drug solution)	Room temperature	Loose spherical agglomerates
	50°C	Spherical agglomerates

Model independent kinetics:

MDT and % DE was evaluated for the all the formulations (table 8) and varied between 3.50 to 5.52 min and 77.52 to 87.08 % respectively.

Though formulation PP3 has relatively higher values of solubility, %CDR, % DE than PP2, the later was selected as an optimized formulation because of its high yield value.

Characterization of Naproxen-polymer agglomerates:

Fourier Transform Infrared Spectroscopy

Infrared spectrum of pure Naproxen is shown in figure 5. The characteristic absorption peaks of Naproxen was obtained at 3188 cm^{-1} due to carboxylic -OH stretch, 3002 cm^{-1} due to aromatic C-H stretch, 2906 cm^{-1} and 2975 cm^{-1} due to aliphatic C-H stretch, 1728 cm^{-1} due to carboxylic C=O stretch and 1604 cm^{-1} due to aromatic C=C stretch.

By comparing the FTIR spectrum of Naproxen with the drug-polymer agglomerates (Figure 5) it was concluded that all the characteristic absorption bands of Naproxen were retained, hence there was no chemical interaction between Naproxen and hydrophilic carriers.

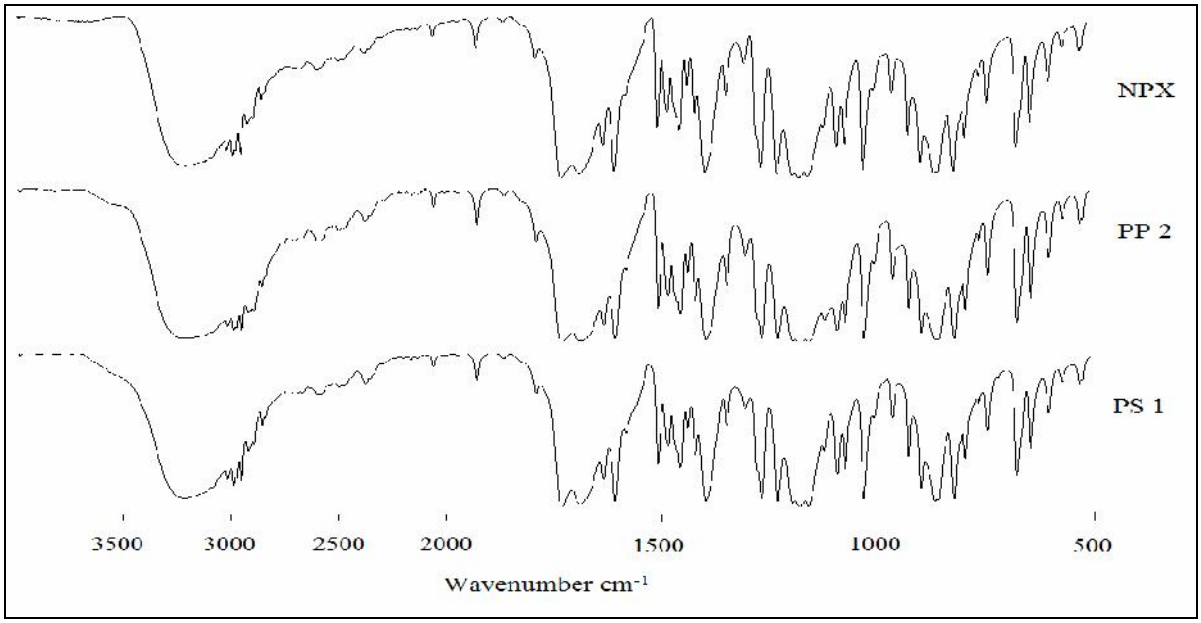

Figure 5: FTIR peaks at different wave numbers of pure naproxen, PP2, and PS1.

Differential Scanning Colorimetry

DSC was used to assess the thermal behaviour of the drug (Naproxen) and its drug-polymer agglomerates prepared. In figure 6, DSC thermogram of Naproxen shows a single sharp characteristic endothermic peak (Tpeak = 159.70^{0}C) corresponding to its melting, indicating its crystalline nature and a single peak indicates that the drug sample is free from impurities.

From the DSC results, a considerable reduction in crystallinity of Naproxen was observed in the prepared drug polymer agglomerates.

X-ray diffraction of powder (XRDP)

X-ray powder diffractometry is a powerful technique for the identification of crystalline solid phases. Every crystalline solid phase has a unique XRDP pattern, which can form the basis for its identification. The X-ray powder diffraction pattern in the 10–60^o, 2θ range showed that the diffraction peaks, characteristic of naproxen were still detectable in the agglomerates (Fig. 7), suggesting that the particles agglomerated in the presence of hydrophilic polymers (PVP K30, PEG 4000 and sodium carboxymethylcellulose) did not undergo structural modifications. However, the differences in the relative intensities of their peaks may be attributed to differences in the crystallinity or particle size of the samples.

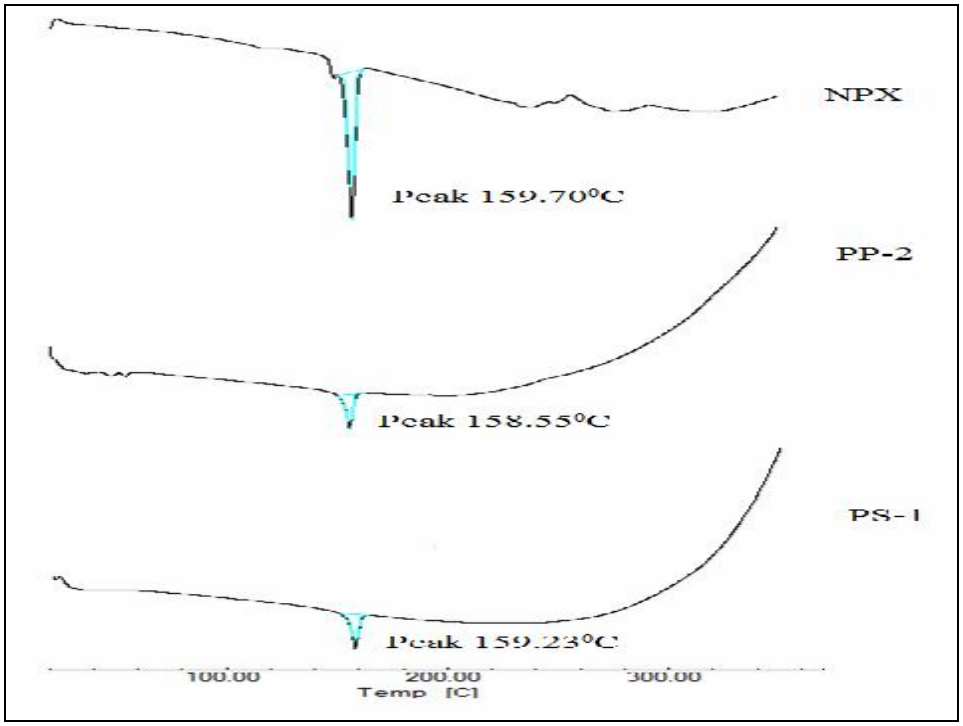

Figure 6: DSC thermographs of pure naproxen, PP2 and PS1.

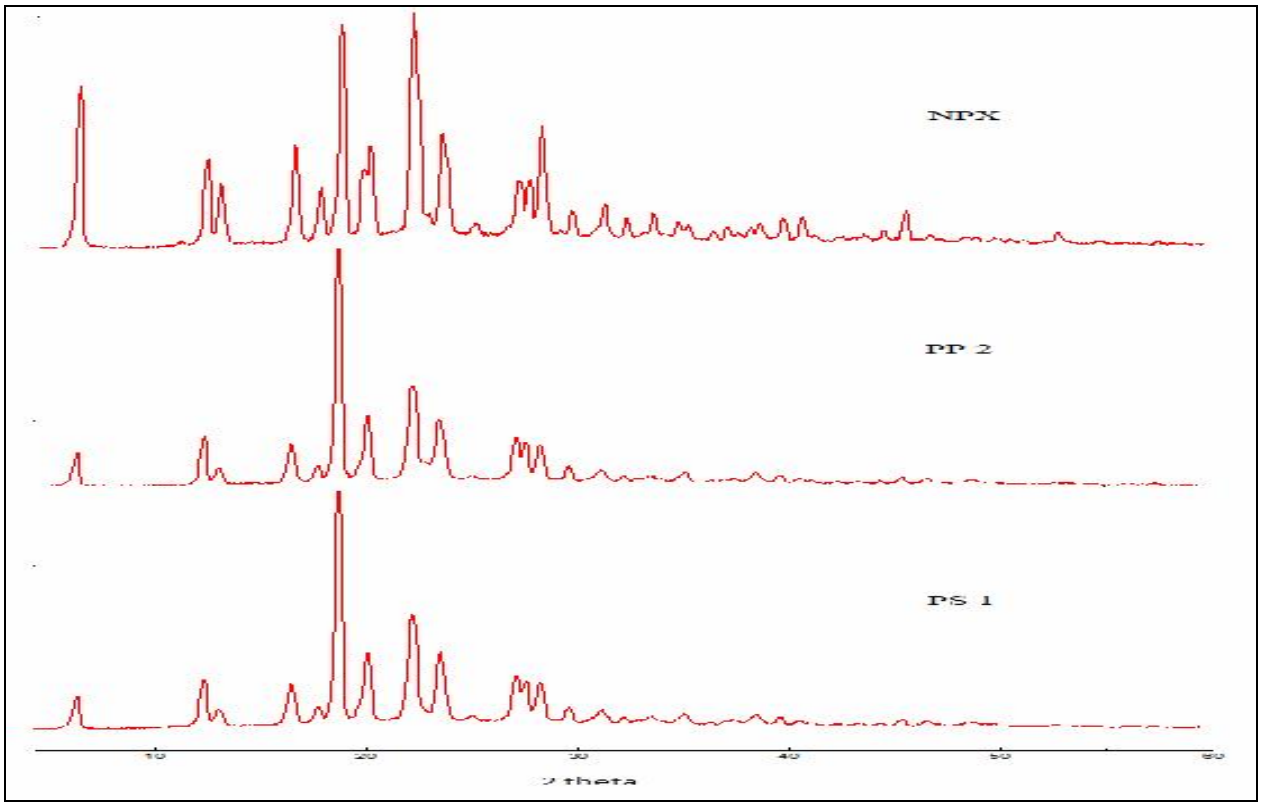

Figure 7: XRD data of pure naproxen, PP2 and PS1.

Scanning Electron Microscopy

SEM of the pure naproxen [figure 8 (A1 & A2)] indicates that the particles have irregular shape with smooth surface whereas drug-polymer agglomerates [figure 8 (B1, B2 & C1, C2)] prepared were spherical in shape with rough surface. It is also found that the pure naproxen particles were markedly smaller in size than the prepared agglomerates.

Scanning Electron Microscopy (SEM):

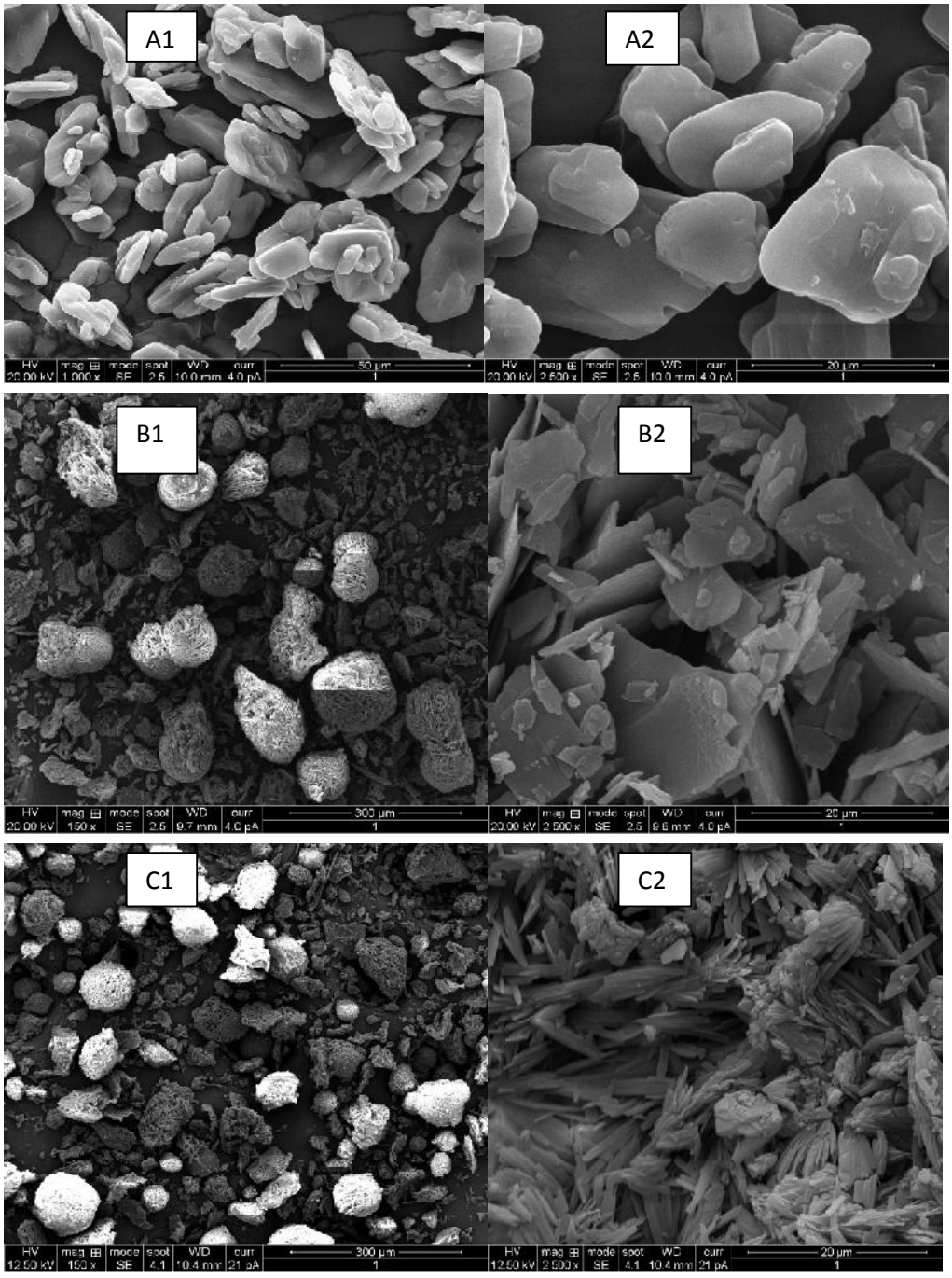

Figure 8: Scanning electron micrographs of appearance (A1, B1, C1) and surface (A2, B2, C2) of naproxen particles: (A) pure naproxen, (B) PP2 and (C) PS1.

Conclusion

Naproxen agglomerates were successfully prepared by CCA technique using hydrophilic polymers like PVP K30, PEG 4000 and Sodium CMC. Spherical agglomerates exhibited improved micromeritic properties compared to pure drug. Formulation, PP2 was selected as an optimized formulation which showed better results with respect to percent drug release (102.9±0.22), percent yield (85.02±0.46), MDT (3.58 min) and % DE (85.65 %) when compared to other formulations. Hence this CCA technique can be used for formulation of tablets of Naproxen by direct compression with directly compressible tablet excipients.

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