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IMPROVEMENT OF DISSOLUTION AND ANTI INFLAMMATORY ACTIVITY TENOXICAM BY SPHERICAL AGGLOMEARATION

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ABSTRACT

Spherical agglomerates of tenoxicam were prepared by the neutralization method with additives (polyethylene glycol 6000, polyvinyl pyrrolidone, and HPMC) using di ethyl ether as a bridging liquid. Prepared agglomerates were evaluated for solubility, dissolution rate and pharmaco dynamic activity, and characterized by SEM, XRPD, DSC and FTIR spectroscopy. Particle size, flowability, solubility, dissolution rate and anti inflammatory activity of plain agglomerates and agglomerates with additives were advantageously improved compared with tenoxicam. XRPD and DSC studies indicated polymorphic transition of tenoxicam during recrystallization but this was not associated with any chemical transition, as indicated by FTIR spectra, well supported by stability studies. Thus spherical crystallization by neutralization method the with selected additives is a satisfactory method for direct tableting of tenoxicam giving improved dissolution rate.

KEYWORDS: XRPD and DSC studies indicated polymorphic transition of tenoxicam during recrystallization but this was not associated with any chemical transition, as indicated by FTIR spectra, well supported by stability studies.

INTRODUCTION

Drug discovery tools like high throughput screening and combinatorial chemistry have contributed to the identification of numerous drugs like compounds that have revolutionized treatment for a variety of clinical indications. Nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs. The efficacy of any orally administered drug usually depends on the dose, solubility and permeability.[1, 2] Discovering

ways to increase the dissolution rate of poorly soluble drugs, in order to improve their pharmaceutical and biological availability still remains one of the major challenging aspects of drug development.[3]

Spherical agglomeration is a novel agglomeration technique involving agglomerate formation based on addition of bridging solvent. It is a particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step. The obtained particles so designed improve the bulk density, flow properties, compressibility, cohesivity, solubility and dissolution rate.[4,5,6]

Tenoxicam is a cyclo oxygenase-II (COX-2) inhibitor used in osteoarthritis, rheumatoid arthritis, and in management of acute pain in adults. It is selective COX-2 inhibitor with 100-fold selectivity for COX-2 relative to COX-1.[7] It shows high anti inflammatory and analgesic activities in addition to low toxicity, moderate incidence of gastric side effects, and high therapeutic index. Tenoxicam is BCS Class II[16,23] drug, practically insoluble in aqueous fluids resulting in dissolution rate limited oral absorption. It is reported to show low and erratic oral bioavailability due to their poor solubility in GI fluids or improperly designed formulations.[7,8] Literature survey reports dissolution enhancement of tenoxicam employing co solvency, solid dispersion, co precipitates and fast release formulation etc.[8,9,10,11] In the present experimental work, attempts were made to enhance the dissolution rate of oxicam derivative like tenoxicam by using crystal habit modification technique by spherical agglomeration. Spherical agglomeration is a particle engineering technique for formation of particles into a spherical form.

Many authors have reported success in improving the dissolution rate by this method for many drugs such as phenytoin, felodipine, celecoxib.[12,13,14] This technique was hence exploited to increase the solubility, dissolution and there by the bioavailability of these drugs.[15] Apart from the improvement in dissolution rate, this technique has been reported for taste masking and particle enlargement.[16,17]

MATERIALS AND METHODS

Tenoxicam was received as a gift sample from Ranbaxy Laboratories Pvt. Ltd., India. The polymers PVP K-30, PEG 4000 and HPMC E5 were procured from SD Fine chemicals, Mumbai, India. HPLC grade methanol, di ethyl ether ortho phosphoric acid and water were purchased from Merck, India. All other reagents used were of analytical grade.

PREPARATION OF TENOXICAM SPHERICAL AGGLOMERATES

About 1 gm of accurately weighed tenoxicam was dissolved in 50 ml of 1N NaOH containing different polymers PVP K-30, PEG 4000 and HPMC E5. The polymers at different concentrations of 0.1%, 0.2%, 0.5% and 1% w/v were used along with drug solution. The system was agitated using a four blade turbine type agitator at 500 rpm at a temperature of 40±1ºC. Precipitation and agglomeration of tenoxicam crystals were brought by gradual addition of 1N HCl with continued agitation for 10 min. A 7.5 ml of diethyl ether was added drop wise and the system was agitated for 15 min at a temperature of 22±1°C. The obtained agglomerates were separated by filtration and dried at 60ºC for 24 hours in a tray dyer. The dried agglomerates were packed in air tight glass containers till further use.[18]

DRUG CONTENT

The tenoxicam samples were analyzed using Waters HPLC system equipped with an auto injector and a UV detector by modifying reported methods (Mason and hobbs, 1995). The assay of drug in formulations was determined by comparison of peak response of test solution against standard solution. System suitability parameters were performed in accordance with USP–NF-30 to confirm the reproducibility of the equipment to be used for the intended analysis.

Accurately weighed pure tenoxicam or formulation equivalent to about 50mg of tenoxicam were extracted with 30ml of mobile phase (disodium hydrogen phosphate 0.02 M: acetonitrile 60:40 v/v, pH adjusted to 4.0 with o-phosphoric acid) by sonication for 20 minutes, diluted with the mobile phase and filtered through 0.45µ membrane filter to get 100mcg/ml standard or test solution. The drug content was determined using Inertsil ODS 3V column (150 x 4.5mm, 5µ) and the chromatograms were recorded at 368nm on the UV detector. The injection volume was 20µl. The drug content in agglomerates was determined by comparison of peak response of test solution against standard solution.[19,20]

SOLUBILITY STUDIES

Solubility of tenoxicam and their agglomerates in water was determined by saturation solubility experiments. An excess amount of tenoxicam (50 mg) was added to 15 ml of water in a 25 ml stoppered conical flask. They were placed on a vibrating shaker and the mixtures were shaken at ambient temperature (25±1ºC) for 24 hours. After 24 hours of shaking, the samples were allowed to equilibrate for another 24 hours. A 2 ml of aliquot samples were

withdrawn and filtered using a 0.45 µ membrane filter. The filtered samples were diluted suitably in pH 7.4 phosphate buffer and assayed for tenoxicam by measuring absorbance at 360 nm respectively using media blank. The solubility experiments were conducted in triplicate and the mean value along with their standard deviations were reported.[21]

DISSOLUTION STUDIES

Dissolution studies of plain drug and agglomerate samples equivalent to tenoxicam 20 mg were conducted in 6.8, 7.4 pH buffers and 0.1N HCl. The in-vitro dissolution study of samples was carried out by dispersed powder technique in a USP apparatus-II (paddle method), using 900 ml of dissolution medium at 37±0.5°C stirred at 100 rpm. Samples of 5 ml were withdrawn at different time intervals. An equal volume of fresh dissolution medium was immediately replaced. The samples were filtered and analyzed spectrophotometrically at 360 nm for tenoxicam. The dissolution of each batch was performed in triplicate (n=3) and mean of all determinations was used to calculate the drug release profile.

OPTICAL MICROSCOPY AND PARTICLE SIZE ANALYSIS

The microscopic observation of tenoxicam agglomerates was performed using optical microscope (Leica microscope, Germany) equipped with a video camera.

Particle size and its distribution for spherical agglomerates were measured by Malvern Master sizer 2000 (Malvern instruments Ltd, Germany). The equipment was set to process from the particle size of 0.05µ to 1000µ. A 5 ml of sample was used for measurement of particle size. Approximately 5% w/v dispersion of agglomerate sample was prepared in liquid paraffin and immediately used for analysis. The air pressure was set at 2.0 bars and the feed rate was set at 50%. The mass median diameter, specific surface area, particle diameter of spherical agglomerates was recorded.

SCANNING ELECTRON MICROSCOPY

The surface morphology and the internal texture of agglomerates were observed by scanning electron microscope (SEM). Beforehand, the samples were mounted on alumina stubs using double adhesive tape, coated with gold in vacuum coating unit and observed in Scanning electronic micro scope (Model JSM 840A, Joel, Japan) at a voltage of 10 Kv. Photomicrographs were taken for each sample at different magnifications.

FOURIER TRANSFORM INFRA RED SPECTROSCOPY

The FTIR spectra of tenoxicam and its agglomerates were obtained. About 5 mg of sample was mixed thoroughly with 100 mg of KBr IR powder and compacted under vacuum at a pressure of about 6000kg/cm² for 3 min. The resultant disc was mounted in a suitable holder in a Schimadzu model 8033 IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 625 cm^{-1} in a scan time of 12 minutes. The resultant spectra were compared for any spectral changes.

P-X-RAY DIFFRACTION

X-ray diffraction pattern of tenoxicam and its agglomerates were obtained on a powder X-ray diffractometer (Seifer 3003TT) using Cu k_{α} radiation at 30 ma and 450 kv. The angular range was set from 0-60° with a step of 0.03/0.5 sec. The relative intensity I/Io and inter planar distance (d) corresponding to 2θ values were obtained and compared.

DIFFERENTIAL SCANNING CALORIMETRY

Differential scanning calorimetric thermo grams of sample were recorded in Mettler Toledo Analyzer equipped with a monitor and printer. The instrument was calibrated with indium as a standard. Accurately weighed 2.5 mg of samples were placed in open flat bottom, pierced aluminium sample pan. Thermo grams were obtained by heating the sample a constant rate 10.00°C/min. A dry purge of nitrogen gas (20ml/min) was used for all runs. Samples were heated from 35°C to 400°C. The melting point, peak maxima, appearance of any new peak and peak shape was noted.

GAS CHROMATOGRAPHY

The residual amount of diethyl ether in spherical agglomerates was determined using Schimadzu gas chromatogram system, equipped with head space sampler and flame ionization detector (Schimadzu). The packed column used for analysis was DB-624 (30m x 0.5mm x 0.5µ), carrier gas was nitrogen, purge gas was air pumped at a pressure of 23 KPa and a velocity rate 0f 3.1 m/sec. The temperature of injector was maintained at 140°C with a detector temperature of 260°C. The temperature programming was started with 40°C with a hold time of 5 min. The temperature was then increased to 240°C at a rate 15°C/min. An accurately weighed 0.5 gm of tenoxicam agglomerates were dissolved in 5ml of dimethyl formamide and transferred in to a head space vial. The sample was analyzed and the chromatogram was recorded.

STABILITY STUDIES

Stability study for the optimized spherical agglomerates of tenoxicam was carried as per ICH guidelines. The samples were stored in amber colored screw capped glass bottles at different temperatures and relative humidity of 37°C/60% RH and 40°C/75% RH for a period of 3 months.[23]

Samples were withdrawn periodically at intervals of 0 month, 1 month, 2 month and 3 month and were visually examined for any physical change. The samples were analyzed for drug content using RP-HPLC. The dissolution studies were conducted for evaluating the alterations in dissolution rate.

IN-VIVO ANTI INFLAMMATORY STUDIES

Preliminary studies for in-vivo anti inflammatory activity of optimized spherical agglomerates of tenoxicam was assessed by carrageenan induced rat paw oedema model.

Male Wistar rats (150 gm-200 gm) were used for the study. Animals were fasted overnight prior to the experiment but water was allowed *ad libitum*. They were divided into standard, test and control groups each containing 6 animals and were labeled as Group-1: Plain drug, Group-2: Spherical agglomerates and Group-3: control respectively. The Group-1 received 4mg/kg of the pure tenoxicam and the Group-2 received the spherical agglomerates equivalent amount of 4mg/kg of tenoxicam. The oral administration was done using 18 gauze needles. To the control group (Group-3) no drug was administered.

Before the administration of carrageenan, a zero hour paw volume was measured for the rats using digital Plethysmometer. After 1hr of drug administration, rats in all the groups were challenged with 0.1ml of 1% carrageenan in the subplantar region of right hind paw by using 26 gauze needles. Paw volumes are again measured at different time intervals of 1, 2, 4, 6, 8 and12 hrs after the challenge of carrageenan. The percentage inhibition of paw volume for each rat in treated groups was calculated and expressed as mean ± SD percent inhibition of paw volume. The single ANOVA test was applied to test the significance.[24]

RESULTS AND DISCUSSION

The spherical agglomerates of tenoxicam were also prepared using neutralization technique. Although the agglomerates were spherical, they did not show enhancement in dissolution.

Hence an attempt was made improve the dissolution by incorporating hydrophilic excipients during the process of agglomeration.

Optimized agglomerates of tenoxicam were evaluated and characterized for drug content, solubility and dissolution rate, optical microscopy, particle size analysis, p-XRD, DSC, FT-IR and GC.

DRUG CONTENT

The optimized spherical agglomerates of tenoxicam were found to be fine, spherical, and easy to handle free flowing powders. The optimized tenoxicam agglomerates showed a drug content of 98.65±0.84%. HPLC chromatograms of standard and test solutions of tenoxicam are shown in figure -1. The percent drug contents of all the spherical agglomerates ensured acceptable content uniformity in each batch and the method of preparation showed no effect on the content uniformity. The drug content indicated that there was no significant loss of drug during the preparation of spherical agglomerates.

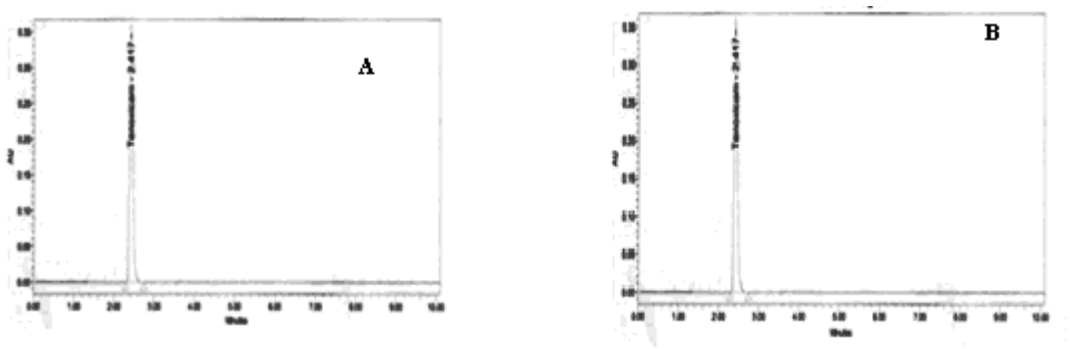

Figure-1: Drug content of spherical agglomerates.

Key: A-tenoxicam standard, B-tenoxciam agglomerates

MICROSCOPY OF SPHERICAL AGGLOMERATES

Microscopy of tenoxicam spherical agglomerates was depicted in Fig-2. Microscopic evaluation reveals that agglomerates were roughly spherical slightly elongated masses with excellent free flowing ability. The agglomerates are poly dispersed with wide distribution of particle size.

The scanning electron microscopy of tenoxicam agglomerates was showing the crystalline changes are observed due to the change in solvent, different temperature conditions and hydrophilic additive. It was assumed that the change in the crystalline nature and incorporation of hydrophilic additive was responsible for dissolution enhancement.

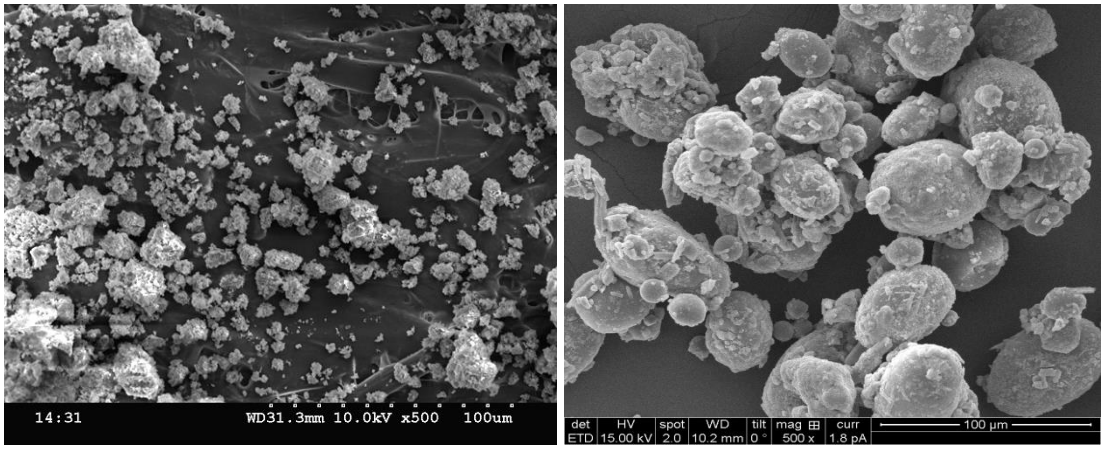

Figure-2 Scanning Electron microscopy of tenoxicam agglomerates under low and high magnification.

PARTICLE SIZE ANALYSIS

The particle size analysis of tenoxicam spherical agglomerates was shown in fig-3. The particle size analysis histograms tenoxicam agglomerates showed bi modal particle distribution indicating the complex particle formation mechanism of spherical agglomerates. The agglomerates were poly dispersed with wide distribution of particle size. The frequency distribution curve is showing an elongation tail towards lowest size ranges exhibiting negative skewness and different parameters were found to be Uniformity-1.031E+00, Particle size range(volume under 50%) 9.00-76.32µm and Specific surface area 2.9688m^2/g.

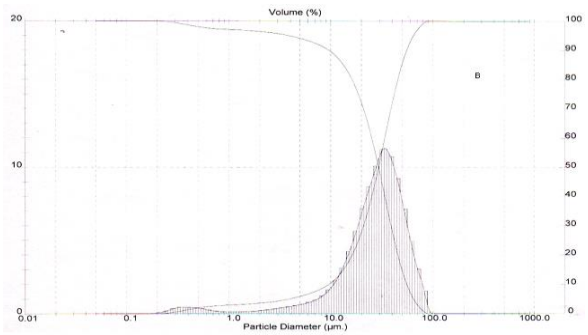

Figure 3: Particle size analysis of tenoxicam agglomerates.

SOLUBILITY STUDIES

Tenoxicam is acidic drug with poor aqueous solubility.[25] Tenoxicam showed an aqueous solubility of 0.021 mg/ml and the agglomerates showed a significant increase in solubility of 0.287mg/ml.

The solubility studies clearly indicate a nearly 8-10 folds increase in solubility of tenoxicam agglomerates when compared to pure drugs. Since the agglomerates were irregularly spherical in shape, the role of improved wettability due to shape factor also cannot be ruled out. The dissolution rate and dynamic solubility usually depends on particle size, particle density and specific surface area. It has been elucidated that the dissolution of agglomerates increases significantly as apparent specific surface area increases. If agglomerated crystals showed change in wettability or crystalline form then dissolution rate increases multifold. Similar results have been reported for celecoxib, mefanamic acid where in a two fold increase in solubility with subsequent increase in bioavailability has been reported by the authors.[14,26]

DISSOLUTION STUDIES

Like many non-steroidal anti inflammatory drug tenoxicam is poorly soluble in water (≈0.01 mg/ml) and show pH dependent solubility, it is thus desirable to conduct pH dependent dissolution studies. Acidic drugs like tenoxicam are absorbed in stomach; hence dissolution studies in 0.1N HCl will give clear indication of its potential bioavailability problems. Similarly, due to its poor solubility in this media, 0.1N HCl can also act as a discriminating medium for evaluating various formulations prepared. Keeping in view all the above considerations, dissolution studies were performed in pH 6.8, 7.4 and 0.1N HCl for tenoxicam formulations.

The drug release from pure untreated tenoxicam was poor and incomplete in all dissolution media studied (figure 4). The release was pH dependent and 20.9% and 25.7% of the drug was released in 0.1N HCl and pH 7.4 respectively in 60 minutes. The drug release in pH 6.8 was better with 40.1% of the drug released in 30 minutes.

To study the effect of hydrophilic excipients and optimize the process, all studies were carried out with official media of pH 6.8. Tenoxicam agglomerates (TEN-SA) did not show significant increase in pH 6.8 buffer when compared to plain drug. At 30 min only 45% of the drug was released which was not significantly different from plain drug. The result was same in all media. In order to achieve an improvement in dissolution rate, hydrophilic additives like HPMC E5, PEG 4000 and PVP K-30 were incorporated.

No significant improvement was obtained with HPMC based tenoxicam agglomerates. On incorporation of PVP and PEG the drug release increased drastically by 2-3 folds. Around 87.5% of drug was released at 30 minutes from PVP based agglomerates, while total drug

was released within 40-45 minutes when PEG was added to the tenoxicam agglomerates (figure 5). Hence, further studies were carried out using PEG as a hydrophilic excipient.

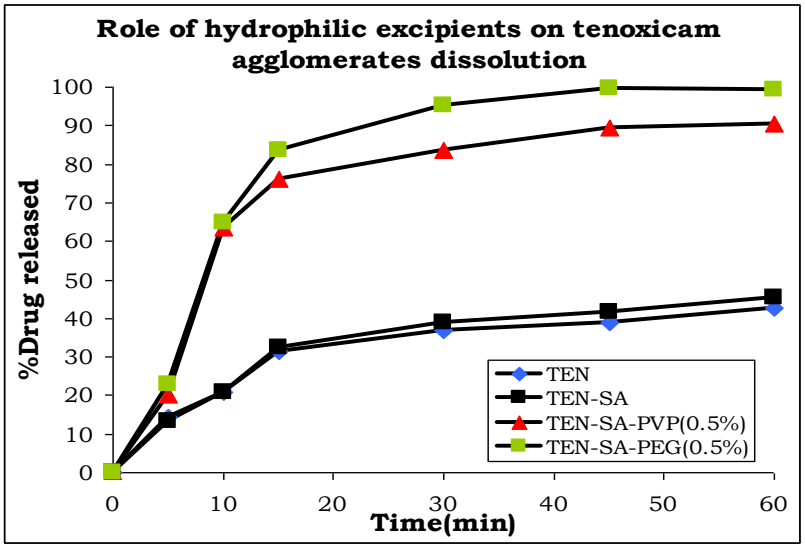

Figure -4: Role of hydrophilic excipients on dissolution profile of tenoxicam agglomerates in pH 6.8 buffer.

KEY: TEN – tenoxicam; TEN-SA – tenoxicam agglomerates without hydrophilic additive; TEN-SA-PEG – tenoxciam agglomerates with PEG 4000; TEN-SA-PVP – tenoxciam agglomerates with PVP.

OPTIMIZATION OF PEG BASED TENOXICAM AGGLOMERATES

The amount of PEG required for agglomeration was optimized. The dissolution rate increased with increase in PEG. At 0.5% PEG level, the drug release from the agglomerate was complete and <95% of drug was released within 30 minutes (figure 5). Beyond this concentration the improvement in release profile was not significant; hence further optimization was carried out with 0.5% of PEG. It was attributed that the hydrophilic additive deposited in the interstitial spaces of agglomerates thus enhancing the wettability and hydrophilic properties of the agglomerate surfaces resulting in enhancement of dissolution.[22,23]

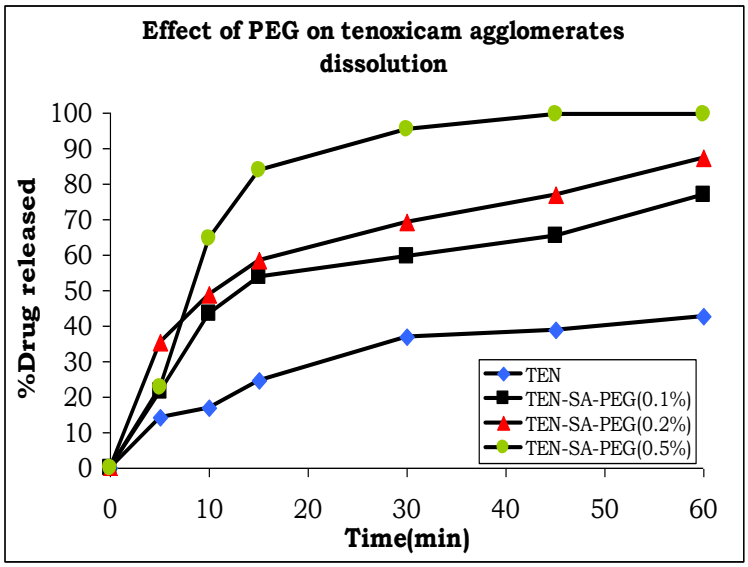

Figure-5 Dissolution profile of tenoxicam spherical agglomerates in the presence of different concentrations of PEG 4000 in pH 6.8.

KEY: TEN – tenoxicam; TEN-SA-PEG – tenoxciam agglomerates with PEG 4000

The dissolution profiles of optimized PEG based tenoxicam agglomerates (TEN-SA-PEG(0.5%) in different media are shown in figure 6. The drug release increased significantly in all media when compared to plain untreated drug. The amount of drug release at 30 minutes was 39.8%, 89.3% and 95.3% in 0.1N HCl, pH 6.8 and 7.4 buffer media respectively. The dissolution profiles of agglomerates in pH 6.8 and 7.4 were similar (f2 = 66), indicative of pH independent release at these pH.

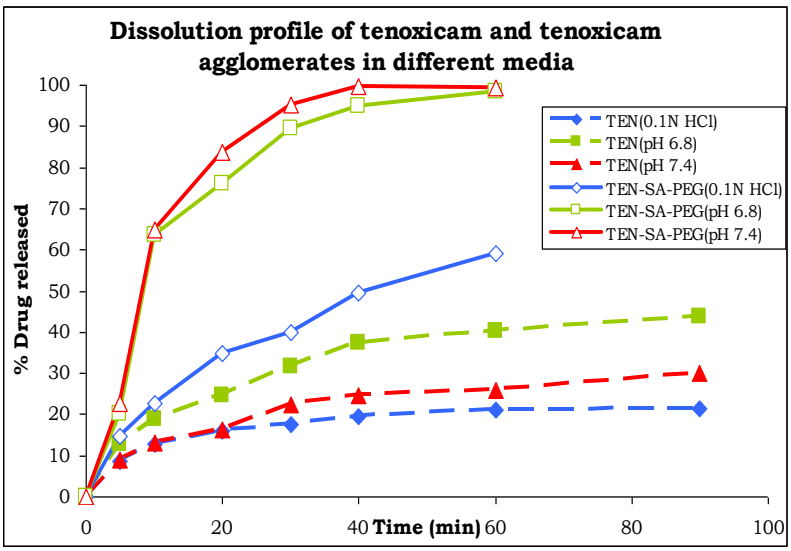

Figure -6: Dissolution profiles of tenoxicam and tenoxicam agglomerates in different dissolution media.

KEY: TEN – tenoxicam; TEN-SA-PEG – tenoxciam agglomerates with PEG 4000 0.5%.

DRUG RELEASE KINETICS

The time taken for drug release of 50% and 70% ($T_{50,}$ T_{70}) for tenoxicam spherical agglomerates in different media was determined and compared with plain drug (table 5.3) to check whether the formulations meets official requirements. Under all media studied, both drug agglomerates showed better dissolution profiles than plain drugs. Similarly a 5 fold increase in the dissolution efficiency at 30 min (DE_{30}) in basic pHs was observed. An improvement in dissolution in 0.1N HCl justifies the objective and the technique used since improvement of drug release in acidic media would improve bioavailability as sufficient drug is made available by the formulation for absorption.

Table-1: Dissolution constants of tenoxicam agglomerates in different media.

pH	Formulation	T_{15} (min)	T_{30} (min)	T_{45} (min)	DE_{30}
0.1 N HCL	TEN	27.28	94.56	165.89	15.89
	TEN-SA-PEG	6.84	22.56	49.45	26.13
6.8 buffer	TEN	22.98	102.82	161.93	12.7
	TEN-SA-PEG	4.89	6.79	10.78	59.36
7.4 buffer	TEN	19.56	92.78	152.8	13.9273
	TEN-SA-PEG	4.76	6.51	13.87	63.68

KEY:, TEN-SA-PEG – tenoxicam agglomerates, T-Marketed = Tenoxicam marketed tablets

The drug release profiles from pure tenoxicam and its spherical agglomerates were fitted to various kinetic models such as zero order, first order and Hixson-Crowell cube root model and their correlation coefficient (r) and release rate constants (K) were calculated and reported (table 3). The pure drug showed the release with highest r^2 value by fallowing first order kinetics. The release of the drug for the optimized formulas of tenoxicam agglomerates followed first order kinetics or cube root law in all pH as seen from the r^2 value. The release kinetics is indicative of Hixson Crowell particle dissolution mechanism based on diffusion model.

FTIR spectroscopy

The FTIR spectrum of tenoxicam (figure 7) was characterized by principle absorption peaks at 3429 cm^{-1}, 3119 cm^{-1} and 3092 cm^{-1} (NH-OH stretching), at 1428cm^{-1} (heterocyclic ring), 1388 cm^{-1}(CH_3 deformation) and 1635 cm^{-1} (amide), 1598 cm^{-1} (C=O) and 1530 cm^{-1} (C=N). A shifting of the characteristic N-H peak due to hydrogen bonding was observed for tenoxicam agglomerates. However the IR spectrum did not show any additional peak

indicating absence of any chemical interaction between tenoxicam with the hydrophilic additive PEG. From the above data it was assumed that a possible physical interaction of drug with polymer was responsible for dissolution enhancement.

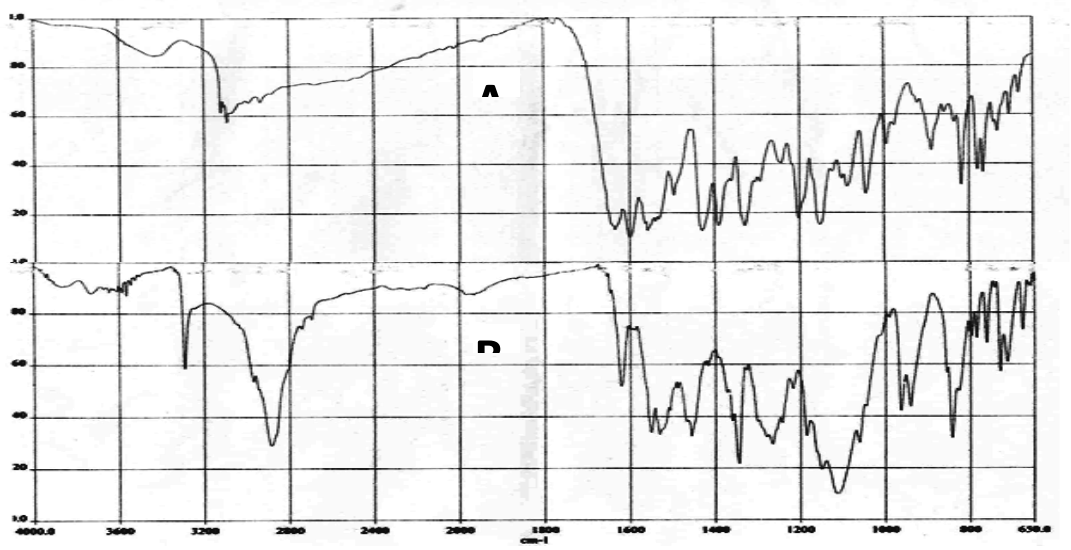

Figure -7: The FTIR spectrum of tenoxicam and its agglomerates.

KEY: tenoxicam(A) tenoxicam agglomerates(B)

p-X-ray diffraction

p-XRD of tenoxicam and tenoxicam agglomerates

The p-XRD pattern of tenoxicam displayed intense, sharp peaks at a diffraction angle (2θ) of 10.96°, 11.8°, 13.03°, 14.54, 16.08, 17.23°, 23.40° and 28.43° indicating its crystalline nature (figure 8). The p-XRD peaks of tenoxicam agglomerates were super imposable with the pure drug, but the spherical agglomerates did not show any significant peaks above the intensity of 200/cps suggesting reduced crystallinity. It was assumed due to incorporation of PEG, the spectra of agglomerates showed partially amorphous form characteristics (peak broadening). These two factors i.e., partial amorphism and reduced crystallinity may have contributed to the enhancement of dissolution rate.

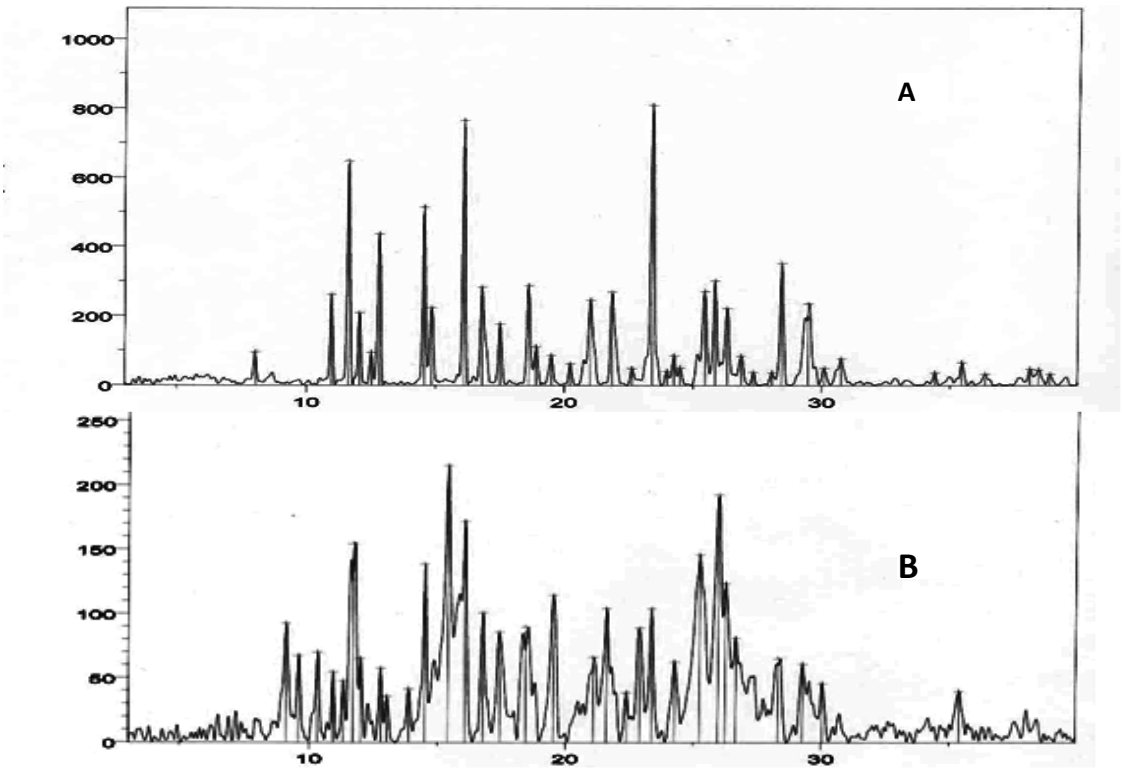

Figure 8 p-XRD of A) tenoxicam B) tenoxicam agglomerates.

Differential scanning calorimetry

The DSC of tenoxicam showed single endotherm corresponding to its high melting point at 215.41ºC due to large crystalline lattice energy (figure 9). Tenoxicam post melting showed degradation exotherm. The DSC scan of tenoxicam agglomerates showed one sharp endotherm at 51°C and another less intense endothermic peak at 210°C corresponding to melting of PEG and tenoxicam respectively. The shift in melting endotherm of tenoxicam agglomerates which was marked by decreased peak sharpness, intensity and broadness could be an indication of drug PEG interaction during the process of agglomeration. The decreased sharpness can also be attributed to the dilution of agglomerates with hydrophilic additive or partial amorphism. This results collaborates with the findings from pXRD data.

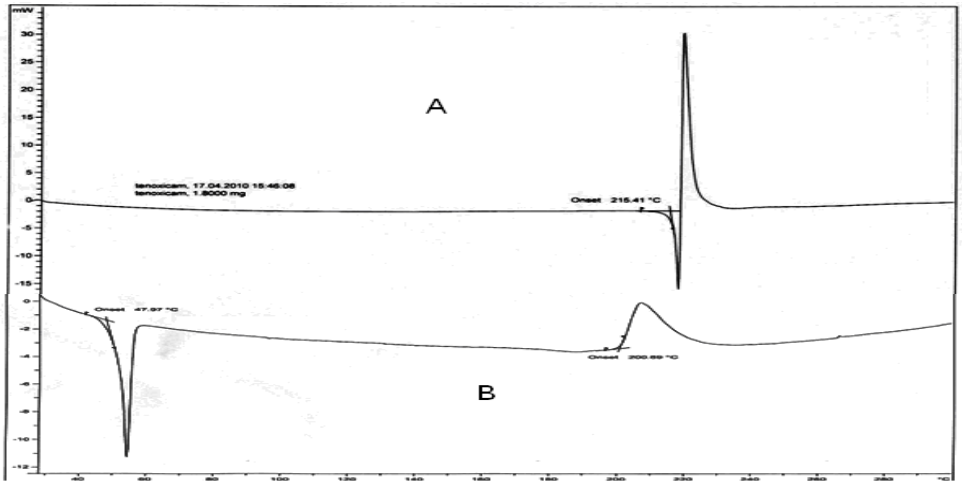

Figure 9: DSC scan of A) tenoxicam, B) tenoxicam agglomerates.

Gas Chromatography

The residual levels of diethyl ether in tenoxicam agglomerates were quantified by gas chromatography (figure 10). The residual concentration of diethyl ether in tenoxicam agglomerates the levels were below detectable limits.

According to the ICH guidelines for residual solvents, diethyl ether is a class-3 solvent and its permissible limits are 5000ppm.[10] The values obtained for the solvent residue in agglomerates is highly below the acceptable limits. Hence, it can be concluded that technique of spherical agglomeration based on neutralization deposition method was efficient in removal of solvents from agglomerates well below permissible levels and was not associated with the drawback of environmental safety.

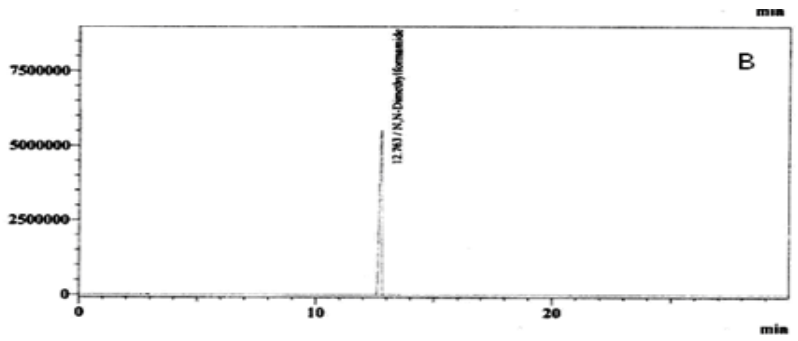

Figure 10: Residual solvent levels in agglomerates by GC.

STABILITY STUDIES

Stability study for the optimized spherical agglomerates of tenoxicam was carried at different temperatures and relative humidity of 25°C/60% RH, 37°C/60% RH and 40°C/75% RH for a

period of 3 months. The drug content was determined by HPLC. The drug content and the release profile did not show any change when stored at room temperature for a period of 3 months. Stability studies data of tenoxicam spherical agglomerates are shown in figure 10 and table 3. The drug was stable in all conditions at end of 3 months as seen by assay results. The percentage of drug released in 7.4 phosphate buffer after 30 min from the spherical agglomerates does not show a significant reduction but the release profile did show alteration when stored at accelerated conditions.

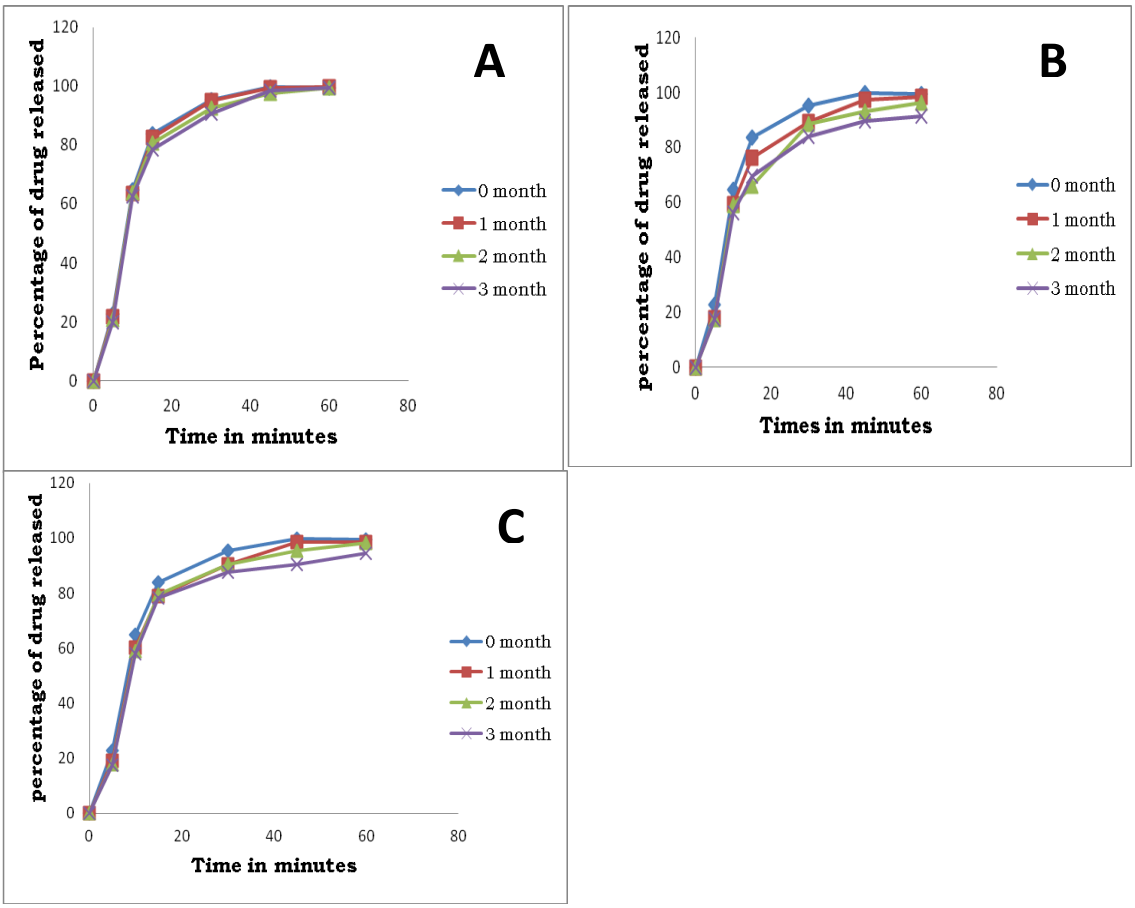

Figure 11: Dissolution studies of tenoxicam agglomerates stability samples.

KEY: A–25°C/60% RH; B–37°C/60% RH; C–45°C/70% RH.

Table 2: Analysis data of tenoxicam agglomerates stability samples.

Months	Drug content (%)			% of drug release in 30 min		
	25°C/ 60%RH	35°C/ 60%RH	40°C/ 75% RH	25°C/ 60%RH	35°C/ 60%RH	40°C/ 75% RH
0	98.65 ±0.54	98.65 ±0.78	98.65 ±0.54	98.65 ±0.54	95.34 ±0.78	95.34 ±0.86
1	98.59 ±0.52	99.12 ±0.65	99.56 ±0.59	98.29 ±0.29	90.45 ±0.96	89.80 ±0.89
2	98.29 ±0.83	99.54 ±0.45	98.65 ±0.34	97.89 ±0.67	90.56 ±0.8	88.456 ±1.08
3	98.29 ±0.67	99.54 ±0.23	99.56 ±0.43	97.64 ±0.32	89.56 ±1.29	87.89 ±1.87

ANTI INFLAMMATORY ACTIVITY

Tenoxicam spherical agglomerates anti inflammatory activity studies are shown in figure 12. The tenoxicam spherical agglomerates showed faster rate of inhibition than the tenoxicam. A peak of inhibition of 26.78% and 47.6% was observed after 2 hour for tenxicam and agglomerates respectively. The difference was significant for the spherical agglomerates showing a significance with a *p* value less than 0.005% (p= 0.04280), indicating that the agglomerates showed an improvement in rate and extent of absorption.

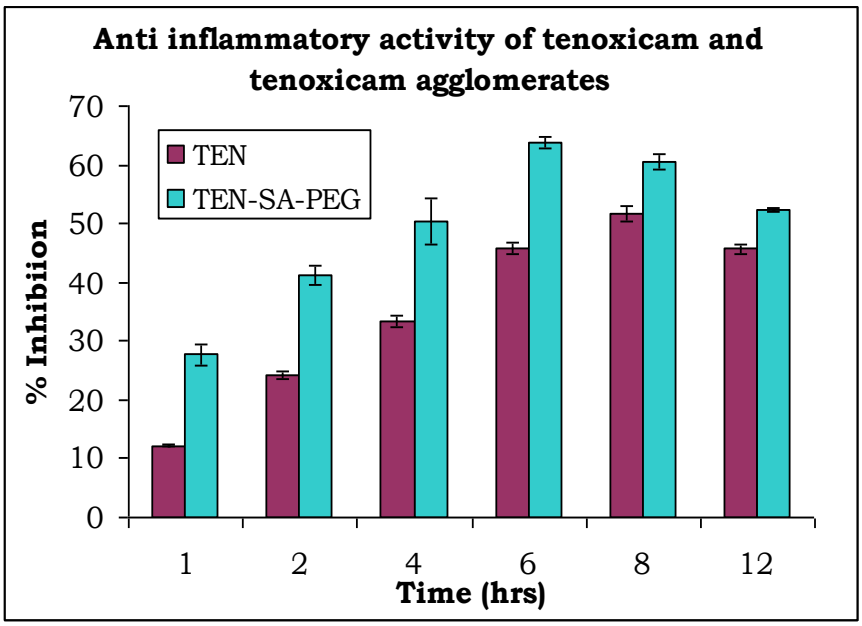

Figure 12: Anti inflammatory activity of Tenoxicam spherical agglomerates.

KEY: TEN- Tenoxicam; TEN-SA-PEG - Tenoxicam spherical agglomerates

CONCLUSION

The spherical agglomeration of tenoxicam by neutralization is a simple and economical method for agglomeration. This method can be effectively used for the dissolution enhancement and improvement in anti inflammatory activity. The spherical agglomeration can be used as one of the method for improvement of particle properties.

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