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Improvement of flowability, compressibility and dissolution of aceclofenac by emulsion solvent diffusion with polyethylene glycol.

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Original Paper

Artículo Original

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Received: 15/12/2011

Accepted: 29/03/2012

ABSTRACT

Aim: The objective behind this study is to improve the compressibility, flowability, packability and dissolution rate of aceclofenac by preparing spherical crystals using quasi emulsion solvent diffusion method.

Materials and Method: Spherical agglomerates of aceclofenac were effectively prepared using acetone, dichloromethane and 0.1 N HCl as good solvent, bridging liquid and poor solvent respectively with different concentrations of polyethylene glycol 6000 in poor solvent.

Results: Prepared agglomerates were spherical with enhanced fragmentation and less elastic recovery. Particle size, flowability, compactibility, packability, solubility and dissolution rate of agglomerates were preferably improved for direct compression compared with raw crystal of aceclofenac. X-ray powder diffraction and differential scanning calorimetry study indicated slight amorphization of drug during recrystallization but not associated with any chemical transition indicated by Fourier transforms infrared spectra.

Conclusion: The present research improved tableting properties and dissolution characteristics of aceclofenac.

KEY WORDS: Spherical crystallization, Compressibility, Polyethylene glycol.

RESUMEN

Objetivo: El objetivo detrás de este estudio es mejorar la tasa de compresión, la fluidez, packability y la disolución de aceclofenaco mediante la preparación de cristales esféricos utilizando el método cuasi emulsión de disolvente de difusión.

Material y Método: Aglomerados esféricos de aceclofenac se prepararon con acetona, diclorometano y ac. HCl 0,1 N que actúan como buen disolvente, líquido aglutinante y mal disolvente respectivamente. En este último caso se añadieron diferentes cantidades de propilenglicol 6000.

Resultados: Los aglomerados esféricos obtenidos se caracterizaron por tener una mayor fragmentación y menor recuperación elástica. En comparación con los cristales originales de aceclofenac, los aglomerados tienen mejores características de tamaño de partícula, fluidez, compactabilidad, empaquetado, solubilidad y velocidad de disolución lo que les hace más adecuados para compresión. Los estudios de difracción por rayos X y calorimetría diferencial de barrido mostraron una pequeña tendencia a formar amorfos durante la recristalización del aceclofenac aunque el estudio mediante espectroscopía infrarroja de Fournier no mostró cambios químicos.

Conclusión: La presente investigación mejora de las propiedades de tabletas y characteristics de disolución de aceclofenaco.

PALABRAS CLAVE: Cristalización esférica, Compresión, Polietilenglicol.

INTRODUCTION

Particle design for solid pharmaceutical dosage form aids in improving the efficiency of manufacturing process. Amongst various types of method employed for tablet preparation, direct compression is found to be an appropriate method of tablet manufacturing. In this process scores of processing steps like granulation and drying process are omitted¹. Some drug crystals demonstrate better compactibility and compressibility which allow the powder bed to compress better. However many drugs are commercially available which exhibit poor flowability and compactibility. In order to overcome such problem, direct compression method has been adopted along with good excipients. The use of spherical crystallization technique appears to be efficient alternative for obtaining suitable particles for direct compression^{2,3}. Spherical crystallization is a particle design technique by which recrystallization and agglomeration can be carried out simultaneously in one step which has been successfully utilized for improvement of flowability and compactibility of crystalline drugs^{4,6}. Various methods are reported in the literature for generating spherical agglomerates such as spherical agglomeration (SA)⁷, quasi emulsion solvent diffusion (QESD)⁸, ammonia diffusion and neutralization⁹. Among which the SA and ESD methods are widely employed¹⁰. Aceclofenac (ACF) is a non-steroidal anti-inflammatory drug used for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, analgesic effects. It is rapidly absorbed after oral administration and peak plasma concentrations are obtained within four h¹¹.

The core venture of this study is to improve the compressibility, flowability, packability, solubility and dissolution rate of ACF by preparing spherical crystals using quasi emulsion solvent diffusion (QESD) method with different concentrations of polyethylene glycol 6000.

MATERIALS AND METHODS

Materials

Aceclofenac (ACF) was a gift from IPCA Ltd, Mumbai. All the polymers used were USP or NF grade: Polyethylene glycol (PEG-6000) was obtained from Central Drug House, India. Acetone and DCM (Dichloromethane) were purchased from Merck, Germany. All the materials used in research work were of analytical grade.

Method:

Development of spherically agglomerated crystals of ACF by QESD method:

In order to prepare spherical agglomerates of ACF, 1 g of drug of original sample was dissolved in 4.0 ml. of acetone at room temperature to get a Quasi-saturated solution at

room temperature. This solution was added to 50 ml of 0.1 N HCl containing 1% / 2% / 3% of PEG-6000 under fixed stirring at 600 rpm and formulation codes were assigned as B, C and D respectively. The formulation without PEG was denoted as A. After 5 min bridging liquid Dichloromethane 1.1 ml was added and stirring was continued for another 20 min. The precipitated crystals were collected by vacuum filtration. The obtained crystals were dried in an oven at 50 °C for 4 h. The dried crystals were stored in desiccators at room temperature. The above process was repeated eight times in order to obtain enough samples for each formulation.

Determination of Yield and Drug content:

Yield of the prepared agglomerates were determined by weighing the agglomerates after drying. For determination of drug content spherical agglomerates of ACF equivalent to 100 mg of ACF were triturated and dissolved in a solvent system containing mixture of 5.2 pH acetate buffer and acetonitrile in a ratio of 3:2. Appropriately diluted samples were filtered through Whatman filter paper 41 (pore size 25 µm) and drug content was determined by HPLC High Performance Liquid Chromatography (HPLC: Shimadzu Corporation, Kyoto, Japan) with 2LC -10AT VP pumps, a variable wavelength programmable UV/VIS Detector SPD-10A VP, a CTO-10AS VP column oven and Inertsil ODS, C18, 250 x 4.6 mm, 5 µ column. The HPLC system was equipped with the software Class -VP series version 5.03. The mobile phase used was a mixture of 5.2 pH acetate buffer and acetonitrile in a ratio of 3:2. The filtered mobile phase was pumped at a flow rate of 1.5 ml/min and the column temperature was maintained at 30 °C. The eluent was detected by a UV detector at 281 nm¹².

Micrometric properties of raw crystals and spherical agglomerates:

Mean particle size of ACF and its agglomerates was determined by randomly counting average diameter of 100 particles with optical microscope and their SEM microphotographs were taken. Bulk density, tap density, Carr's index¹³ and angle of repose¹⁴ were determined (table 1).

Compressibility study:

The Heckel study was performed by compressing 500 mg of raw crystals and spherical agglomerates on hydraulic press (Samrudhi Enterprises, Mumbai, India.) using 13 mm flat faced punch and die set, at pressure 20, 30, 40, 60, 80, 100 and 120 kN and thickness, weight and diameter of compacts were determined. Heckel parameters were determined using Heckle equation as given below^{15,16}.

$$\ln (1/1-D) = KP + A$$

Where, D is the relative density of powder for applied pressure P . The slope of the straight-line portion K is the reciprocal of the mean yield pressure (MYP) of the material. From the value of the intercept A , the relative density D_a , D_o and D_b can be calculated using following equations.

$$D_a = 1 - e^{-A}$$

$$D_o = 1 - e^{-A_0}$$

$$D_b = D_a - D_o$$

For determination of ER thickness of the compact of agglomerates and raw crystal of ACF was determined at compression pressure 60 kN and at 24 h (table 2) after releasing the tablet using following equation¹⁷.

$$ER = [(t_2 - t_1) / t_1]$$

Where t_1 is the minimal thickness of the powder bed in the die and t_2 is the thickness of the recorded tablet.

Packability determination:

In packability determination 25 g of sample was poured slowly and gently into a 25 ml measuring cylinder and tapped for 100, 200, 300, 400, 500, 600, 700, 800, 1100 and 1200 times. The Stampfvolumeter measurements allow calculations of the compactibility and cohesiveness values via modified Kawakita's equation and Kuno's equation¹⁸.

Solubility study:

Solubility of raw crystals and spherical agglomerates of ACF were determined in pH 7.4 phosphate buffer. Excess amount of sample were added in 20 ml of pH 7.4 phosphate buffer and was continuously shaken (300 rpm) at $25 \pm 0.5^\circ\text{C}$ for 48 h and sonicated using sonicator (Dolphin™) for 2 h. Samples were filtered through 0.45 μm analyzed by HPLC for drug content.

Scanning Electron Microscopy (SEM)

Agglomerates were coated with a thin gold-palladium layer by sputter coater unit (VG- Microtech, United Kingdom), and the surface topography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (SEM; Cambridge, United Kingdom) operated at an acceleration voltage of 10 kV.

X-ray powder diffraction (XRPD):

X-ray powder diffraction of raw crystals and spherical agglomerates (With 3% PEG) were analyzed by Philips PW 1729 x-ray diffractometer. Samples were irradiated with monochromatized Cu K_α -radiations (1.542 \AA) and analyzed between $2-55^\circ$ (2θ). The voltage and current used were 30kV and 30 mA respectively. The range was 5×10^3 cycles/s and the chart speed was kept at 100 mm/ 2θ .

Differential Scanning calorimetry (DSC):

Thermal properties of raw crystals and spherical agglomerates of ACF (With 3% PEG) were analyzed by DSC (TA instrument:DSC Q20 V24.4 Build 116). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as the purge gas through DSC cell at flow rate of 50 ml per min and 100 ml per min through the cooling unit. The sample (8 mg) was heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 0 to 200°C at a heating rate of $10^\circ\text{C}/\text{min}$.

Fourier transforms Infrared spectroscopy (FT-IR):

Fourier transforms Infrared spectroscopy of raw crystals and spherical agglomerates of ACF (With 3% PEG) was recorded using Perkin Elmer (INDIA) FT-IR system using potassium bromide (KBr) pellet method. Each spectrum was derived from single average scans collected in the region 4000 to 400 cm^{-1} .

In Vitro dissolution studies:

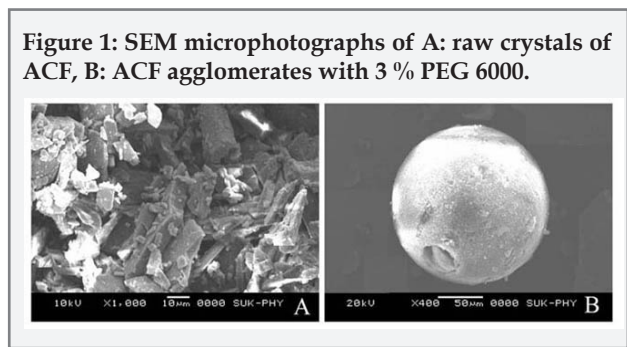
The dissolution studies raw crystals and spherical agglomerates of ACF were performed by using USP paddle type 3 stage dissolution rate test apparatus (SECOR INDIA) in 900 ml of pH 7.5 phosphate buffer. Temperature was maintained at $37 \pm 2^\circ\text{C}$ and 100 rpm stirring was provided for each dissolution study. ACF and its spherical agglomerates equivalent to 100 mg of ACF were used for each dissolution study. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41 (pore size 25 μm), concentration of ACF was determined by HPLC as specified in yield and drug content.

RESULTS AND DISCUSSION:

Development, micromeritic properties and solubility of ACF agglomerates:

ACF is highly soluble in acetone, soluble in dichloromethane but completely insoluble in 0.1 N HCl¹¹, so acetone, dichloromethane and 0.1 N HCl were selected as good solvent, bridging liquid and poor solvent respectively. Formation of lumps, agglomerates of un-uniform size and shape was observed at lower stirring rates, while high stirring rate destroyed the agglomerates, an optimum was found to be 600 rpm.

When solution of drug in good solvent was poured into poor solvent the quasi-emulsion droplets of drug solution were produced initially. Successively crystallization of the drug occurred at the outer surface of the droplet. The agglomerates formed were spherical (figure 1) in nature.



The yield of agglomerates were found to be 91,92 , 90 % and drug content 89.92, 90.76, 94 % for formulation B, C and D respectively. It was found that size of agglomerate with different polymer concentration was increased 9 to 10 times (table 1) as compared to raw crystals. Particle size of the agglomerates increased due to the presence of a cohesive layer of bridging liquid on the surface of growing. The bulk density agglomerates with PEG was lower than raw crystals of ACF. Reduction in bulk densities of spherical agglomerates indicates the greater porosity within the agglomerates. Similar results were also obtained by Ali N et al, 2007¹⁹. Lower values of Carr’s index, Hausner’s ratio and angle of repose (table 1) for all agglomerated formulation showed its better flowability than raw crystals of ACF¹⁴. Agglomerates showed significantly higher solubility (table 1) than raw crystals of ACF may be due to improved porosity, decreased primary particle size and amorphization of drug in agglomerates as demonstrated by DSC and XRD studies.

Compressibility and Packability:

Heckle parameters D_a , D_o , D_b , MYP, ER and packability parameters a, b, k of raw crystals and spherical agglomerates of ACF are given in table 2. The D_b values for all spherical agglomerates were higher than the raw crystals of ACF indicates that the agglomerates are highly fractured during early stage of compression although fragmentation is followed by plastic deformation. The results were well supported by higher MYP values. The elastic recoveries of the compacts of plane agglomerates and agglomerates with PEG 6000 were smaller than that of raw crystals of ACF. These findings suggested that the agglomerated crystals were easily fractured, and the new surface of crystals produced might contribute to promote plastic deformation under compression. It was found that for all agglomerates value of parameter a in Kawakita’s equation reduced and respective parameters b and k in Kawakita’s and Kuno’s equation increased compared with those of raw crystals of ACF. It suggests that during tableting these agglomerates were flow smoothly from the hopper into die cavity to attain uniformity in weight and is necessary in direct tableting. This improvement in packability and flowability is attributed to size enlargement and spherical shape of these agglomerates.

XRD, DSC and FTIR study:

XRD, DSC and FTIR spectra of drug and agglomerates with 3% PEG are shown in figure 2, 3 and 4 respectively were identical. It has indicated that no any polymorphic transition has occurred during crystallization ACF which

Table 1. Micrometric properties and solubility of ACF and its spherical agglomerates (n = 3).

FC	Diameter (µm) n=100	Angle of repose (°)	Bulk density (g/cc)	Carr’s Index (%)	Solubility (µg/ml) pH 7.4 PB
A	16.7 ± 1.05	52.23 ± 0.75	0.322 ± 0.007	32.35 ± 0.5	109.05 ± 2.3
B	151.5 ± 0.81	23.14 ± 0.65	0.281 ± 0.006	15.01 ± 0.4	227.84 ± 3.1 **
C	162.3 ± 1.13	22.23 ± 0.75	0.279 ± 0.006	14.15 ± 0.6	268.27 ± 2.1 **
D	158.7 ± 1.19	23.23 ± 0.29	0.275 ± 0.008	14.06 ± 0.7	408.96 ± 4.3 **

FC: Formulation Codes, PB: Phosphate Buffer.

** represents significantly different from the value for raw crystals of ACF at p < 0.001.

Table 2. Heckel parameters: D_a , D_o , D_b , MYP (mean yield pressure), ER (elastic recovery), Kawakita constants a, b and Kuno’s constant k of raw crystals and spherical agglomerates of ACF.

FC	D_a	D_o	D_b	a	b	k	MYP	% ER
A	0.617 ± 0.003	0.416 ± 0.011	0.201 ± 0.007	0.430 ± 0.06	0.003 ± 0.0005	0.0026 ± 0.001	22.54 ± 2.4	8.1 ± 1.2
B	0.564 ± 0.003***	0.181 ± 0.004***	0.383 ± 0.003***	0.288 ± 0.06	0.012 ± 0.004	0.0102 ± 0.004	25.31 ± 1.6 **	4.8 ± 0.4 ***
C	0.483 ± 0.005***	0.161 ± 0.008***	0.322 ± 0.003***	0.288 ± 0.03	0.010 ± 0.006	0.0105 ± 0.006	28.31 ± 2.3**	5.1 ± 0.6***
D	0.570 ± 0.002***	0.176 ± 0.003***	0.394 ± 0.004***	0.278 ± 0.02	0.021 ± 0.003	0.011 ± 0.003	26.31 ± 1.5**	5.0 ± 0.5***

FC: Formulation Codes.

***, **, * represents significantly different from the value for raw crystals of ACF at p < 0.001, p < 0.01 and p < 0.05 respectively.

Figure 2: X-ray powder diffraction pattern of A: raw crystals of ACF, B: ACF agglomerates with PEG 6000.

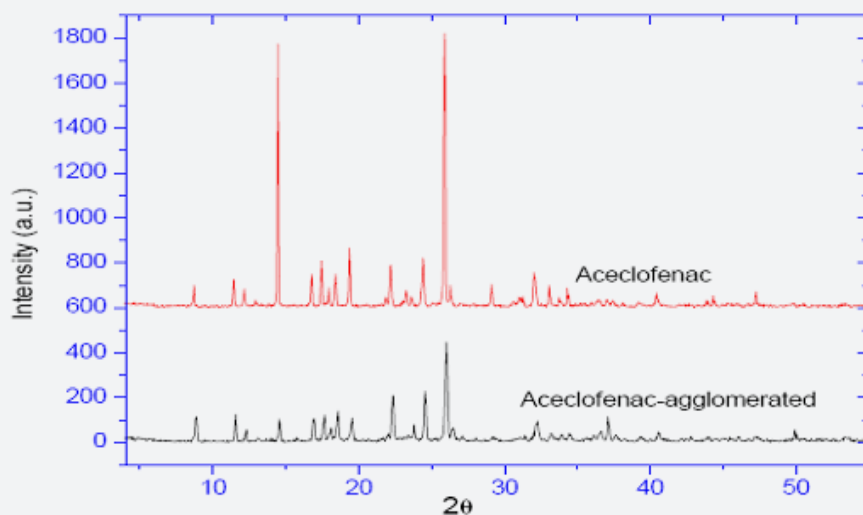


Figure 3: DSC thermogram of A: raw crystals of ACF, B: ACF agglomerates with PEG 6000.

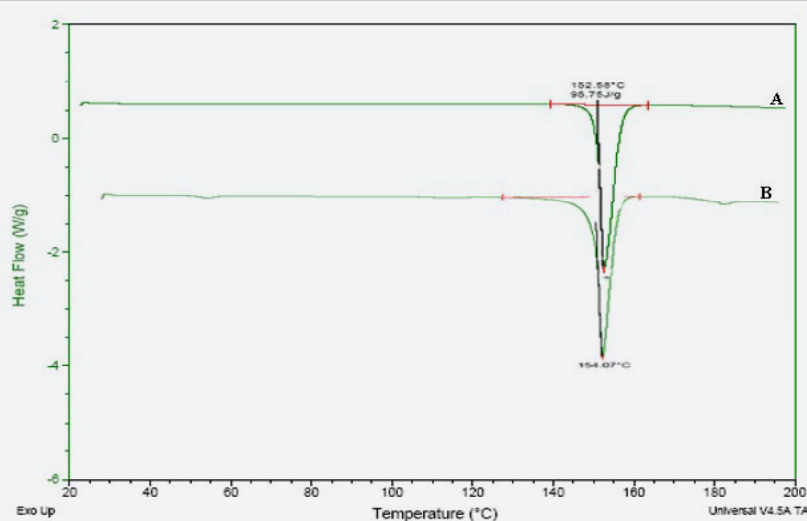


Figure 4: IR Spectra of A: raw crystals of ACF, B: ACF agglomerates with PEG 6000

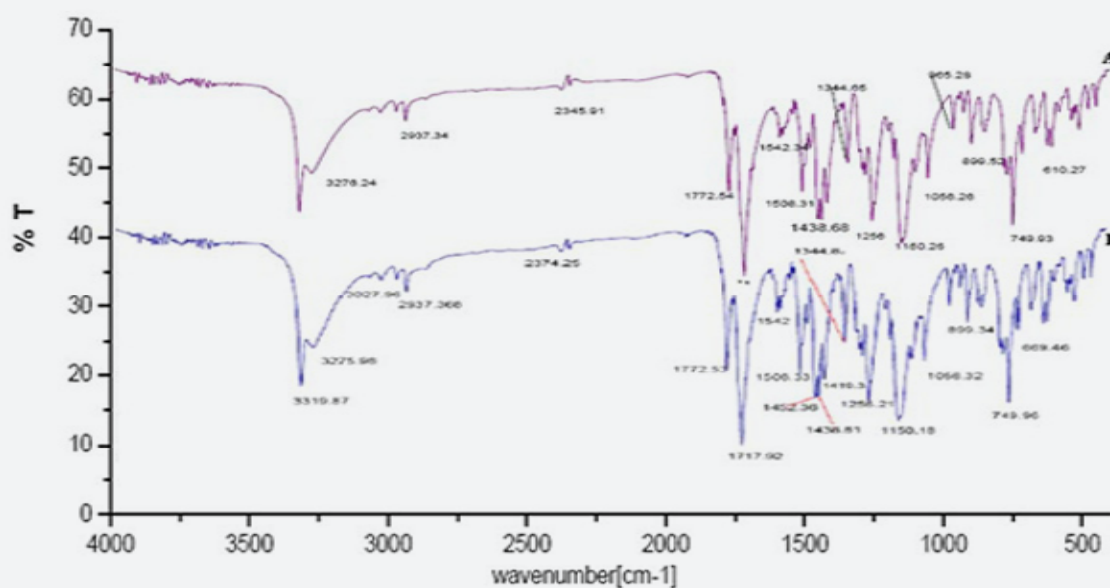
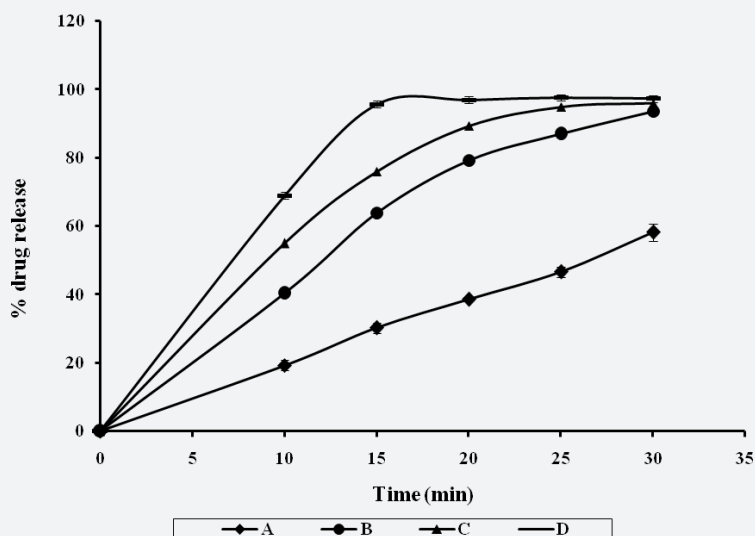


Figure 5: In vitro dissolution study of A: raw crystals of ACF, B: ACF agglomerates with 1 % PEG 6000, C: ACF agglomerates with 2 % PEG 6000. D: ACF agglomerates with 3 % PEG 6000.



reveals stable nature of drug during agglomeration process. The reduction in intensity (in XRD) and decrease in enthalpy in DSC) of the agglomerate has indicated modest amorphization of drug in the agglomerates.

***In vitro* Dissolution study:**

All spherical agglomerates showed higher dissolution rate rather than control drug crystals (figure 5). Agglomerates with PEG 1, 2 and 3% has shown 90% drug release within 30, 20 and 15 min respectively while for raw crystal of ACF it was more than 45 min. Thus PEG is supposed to increase the dissolution ACF in agglomerate with increasing concentration may be due to increase in hydrophilicity. Also the presence of bridging liquid enhances the wettability of crystallized product which also believed to promote the dissolution rate.

CONCLUSION

ACF agglomerates prepared by emulsion solvent diffusion method were dense with great mechanical strength and showed improved flowability, compactibility, packability, solubility and dissolution rate compared with raw crystals. Incorporation of PEG-6000 during agglomeration significantly enhanced the solubility and dissolution rate of ACF may be due to increased wettability and slight amorphization. Thus present work offers promises as a simple, rapid and economic technique for the improvement of tableting properties and dissolution rate of aceclofenac.

ACKNOWLEDGMENT

The authors are thankful to Head of the Department, University Department of Pharmaceutical Sciences, Utkal University, Vani Vihar, Bhubaneswar, Orissa, India for providing necessary research facility.

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