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INTRODUCTION Oral drug delivery is the most widely applicable administration route among all other drug administration routes such as nasal, ophthalmic, rectal, transdermal, and parenteral routes. It has been explored for systemic delivery of drugs via pharmaceutical products of a different dosage form1. The majority of the pharmaceutical products designed for oral delivery are immediate release or conventional release systems for rapid drug absorption2. Conventional dosage forms have various limitations to deliver the dosage form via the oral route, such as poor patient compliance, increased chances of dose missing of a drug with a short half-life for which frequent administration is necessary3.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of a controlled drug delivery system that could revolutionize the method of medication and provide several therapeutic benefits4. Controlled drug delivery systems have been developed to control the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drugs to tissues5. Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories: delayed release, sustained release, site-specific targeting, and receptor targeting6.

A controlled drug delivery system is usually designed to deliver the drug at a particular rate. Safe and adequate blood levels are maintained for a period as long as the system continues to deliver the drug7. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient8. The introduction of matrix tablets as the sustained release (SR) has given a breakthrough for novel drug delivery systems (NDDS) in pharmaceutical technology9.

It excludes complex production procedures such as coating and palletization during manufacturing, and the drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations10. The hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complications and expense involved in the marketing of new drug entities, it has focused greater attention on developing sustained release or controlled release drug delivery systems11.

Matrix systems are widely used for sustained release. It is the release system that prolongs and controls the release of the dissolved or dispersed drugs12. A matrix is a well-mixed mixture of one or more drugs and a gelling agent, such as hydrophilic polymers. The sustained release approach allows for therapeutically efficient

accumulation in the systemic circulation over a more extended period, resulting in improved patient compliance13.

Many SR oral dosage forms have been developed, including membrane-controlled systems, matrix with water-soluble/insoluble polymers or waxes, and osmotic systems. Recent research has concentrated on the designation of SR systems for poorly water-soluble drugs14. The lipid waxes and related materials prepare the lipid matrix. In this system, the active compound is contained in a hydrophobic matrix that remains intact during drug release15.

The release of the active substance depends on the aqueous medium dissolving the conduit, which is released from the solids, forming a porous matrix of tortuous capillaries. The active substance dissolves in the aqueous medium and diffuses out of the matrix by way of the water-filled capillaries16. The materials used as matrix formers include hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated soy oil, microcrystalline wax, carnauba wax, as well as hydroxypropyl methylcellulose (HPMC)17.

Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins18. The drugs inhibit the synthesis of the inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor (TNF) and prostaglandin E2 (PGE2) production. Effects on cell adhesion molecular from neutrophils have also been noted. In vitro data indicate inhibition of cyclooxygenase (COX)-1 and 2 by aceclofenac in whole blood assays, with selectivity for COX-2 being evident19. Aceclofenac is a perfect applicant for a sustained release tablet.

It reduces the frequency of drug administration and improves bioavailability, and increases patient compliance20. Aceclofenac has a short biological half-life of 2-4 hours; thus, it does not show the pharmacological effect for a long time21. Sustained-release tablets have the properties to release slowly, and they maintain the bioavailability of drugs for a long time. Therefore, in this study, we made a sustained release tablet of aceclofenac and determined all in vitro parameters of sustained-release tablets.

MATERIALS AND METHODS Materials The material used were aceclofenac (Sigma-Aldrich), HPMC K15M, Guar gum, lactose, polyvinylpyrrolidone (PVP) K-30, isopropyl alcohol (IPA), talc, magnesium stearate, phosphate buffer pH 6.8, HCl, distilled water, and KBr. The instruments used include melting point apparatus, water bath shaker, UV spectrophotometer (Labindia), Fourier Transform Infrared (FTIR) Spectroscopy (Shimadzu), sieve #10, #18, #40, digital analytical balance, micromeritics instrument, micrometer (Mitutoyo), Monsanto tablet hardness tester, Roche friabilator, and dissolution apparatus type 1 basket. Methods The study was divided into three

stages: preformulation, granule preparation-evaluation, and tablet formulation-evaluation.

Each stage consists of several tests and evaluations. The method flow chart is presented in Figure 1. / Figure 1. Flowchart for sustained release tablet preparation and evaluation parameters Physical appearance Aceclofenac powder was poured on light and dark backgrounds, and its physical appearance was observed. The results were compared with standard references22. Determination of melting point The melting point of the aceclofenac was determined by the capillary fusion method. A one-sided closed capillary was filled with drug and placed into the Remi's melting point apparatus.

The temperature at which solid drug converted into liquid was recorded and compared with standard references22. Solubility studies The solubility of Aceclofenac was tested in different solvents. The drug (50 mg) was dissolved in 10 ml of solvent in a 10 mL solubility bottle. The bottle was adequately covered with a lid and placed in the water bath shaker maintained at 37°C for 24 hours. Samples were taken manually and filter through 0.45 µm filter paper. The UV absorbance of the solution was recorded using a UV spectrophotometer after suitable dilutions at 273.5 nm23.

Compatibility study of drug and polymer (FTIR) The sample was mixed with a suitable amount of KBr and converted into pellets using KBr press at 15 tons hydraulic pressure. The IR scanning of samples was done in between 4000 and 400 cm-1 and spectrum observed for any occurrence and disappearance of characteristic drug peak and compared with the standard references23. Tablet preparation The tablet formulation was carried out by varying the matrix formers: HPMC and Guar gum. In total, there were nine formulas for tablets, as shown in Table I.

The corresponding amounts of the drug were accurately weighed and passed through the #40 sieve. The corresponding amounts of polymers (HPMC/Guar gum) and lactose were accurately weighed, screened through screen #40. The screened mass was transferred into a clean and dry mortar and mixed gently for 5 minutes. Alcoholic solution (IPA) of PVP K 30 (5% w/v) was added to the powder mixture blended to form a wet mass. The wet mass was passed through sieve no. #10 and the resulting granules were placed on a tray for drying into the oven at 50°C for 10 minutes. The dried granules were passed through sieve no—#18.

The corresponding magnesium stearate and talc were accurately weighed and then mixed with dried granules for 3 minutes. The granules were compressed into tablets using a single station hand operated tablet compression machine, and the tablets were collected23. Table I. Composition of the sustained release matrix tablets containing

aceclofenac Materials (mg) _Formula _ _ _F1 _F2 _F3 _F4 _F5 _F6 _F7 _F8 _F9 _ _Aceclofenac _200 _200 _200 _200 _200 _200 _200 _200 _200 _ _HPMC _50 _100 _150 _200 _- _- _- _- _100 _ _Guar gum _- _- _- _- _50 _100 _150 _200 _100 _ _Lactose _200 _150 _100 _50 _200 _150 _100 _50 _50 _ _PVP K30 _25 _25 _25 _25 _25 _25 _25 _25 _25 _ _IPA _q.s. _q.s. _q.s. _q.s. _q.s. _q.s. _q.s. _q.s. _q.s.

_ _Talc _20 _20 _20 _20 _20 _20 _20 _20 _20 _ _Mg Stearate _5 _5 _5 _5 _5 _5 _5 _5 _5 _ _ Determination of bulk density Bulk density was defined as the mass of the powder divided by the bulk volume and expressed as g/cm3. It depends upon particle size distribution, particle shape, and particle adhere. Apparent bulk density was determined by pouring the blend into a 10 mL graduated cylinder and calculated based on the equation as reported by Yasmin et al24. Determination of tapped density The measuring cylinder containing a known mass of powder blend was tapped 100 times using density apparatus. The minimum volume occupied by the powder in the cylinder was measured.

The tapped density was calculated based on the equation as reported by Yasmin et al24. Determination of angle of repose The angle of repose (?) was determined using the funnel method. Briefly, the powder blend was poured through a funnel that can be raised vertically until a maximum cone height was obtained. The radius of the heap was measured, and the angle of repose was calculated based on the equation as reported by Yasmin et al24. The values of angle of repose indicating flow properties have been recommended as <25 indicating excellent flow, 25-30 indicating good flow, 30-40 indicating passable, and >40 indicated the very poor flow.

Determination of compressibility index Determination of compressibility index was the simplest way to measure the flow property of powder to determine its compressibility. Compressibility index indicates the ease with which a material could induce flow, which was calculated using the equation as reported by Yasmin et al24. The values of compressibility index indicating flow properties have been recommended as <12 indicating excellent flow, 12 – 16 indicating good flow, 18 – 21 indicating fair to passable, 25 – 35 indicating poor, 33 – 38 indicating very poor, and >40 indicated the extremely poor flow. Determination of Hausner's ratio Hausner's ratio was an indirect index of ease of powder flow. Density determinations were used to calculate the Hausner's ratio using the equation as reported by Yasmin et al24.

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25). Examination of tablet appearance Twenty tablets of each formulation were randomly taken and examined to check any physical or surface roughness in the tablets. Determination of tablet thickness Tablet thickness was an essential parameter in reproducing appearance and also in counting by suing filling equipment. Many tablet

filling/packaging equipment utilizes the uniform thickness of the tablets as a counting mechanism25. In the present study, 10 tablets were randomly selected, and their thickness was recorded using a micrometer.

Determination of uniformity of weight The weight variation test would be a satisfactory method of determining the drug content uniformity. USP procedure for uniformity of weight was followed. The allowed weight variation limits were 10%, 7.5%, and 5% for tablets having weight 130 mg or less, 130-324 mg, and >324 mg, respectively26. Briefly, 20 tablets were taken and weighed individually and collectively using a digital analytical balance. The average weight of one tablet was determined from the collective weight. Determination of tablet hardness The hardness of the tablet was defined as the force applied across the diameter of the tablet to break it.

The resistance of a tablet to chipping, abrasion, or breakage under the condition of storage, transportation, and handling before use depends on its hardness or strength27. For the determination of tablet hardness, 10 tablets from each batch were randomly selected, and hardness was determined using Monsanto tablet hardness tester. Determination of tablet friability The friability of the prepared tablets was determined using Roche friabilator.

This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at the height of 6 inches in each revolution. Previously weighed, 20 tablets were placed in the friabilator and subjected to 100 revolutions. Tablets were de-dusted using a soft muslin cloth and re-weighed. The percentage friability was determined using the equation as reported by Ahmed et al28. Determination of drug content Six tablets from each batch were weighed and finely powdered using a clean and dry mortar and pestle.

Powder equivalent to the weight of one tablet was transferred to a 100 mL volumetric flask and shaken with 60 mL of phosphate buffer for 10 minutes. The volume of the resulting solution was made to 100 mL and kept for 24 hours. After 24 hours, the content was filtered. An aliquot of 1.0 mL from the filtrate was diluted to 100 mL with phosphate buffer in a volumetric flask, and then further 1 mL from this solution was diluted up to 10 mL phosphate buffer in a 10 mL volumetric flask29.

The sample was analyzed by a UV spectrophotometer at 273.5 nm. Determination of in vitro dissolution profile The in vitro dissolution studies were carried out in the USP tablet dissolution test apparatus, type 1 (basket). As much as 900 mL of phosphate buffer (without enzymes) was used as a dissolution medium. Dissolution studies were carried out for 24 hours. The temperature of the dissolution medium was maintained at

37±0.5°C. The paddle was rotated at 75 rpm. Sample (5 mL) was withdrawn data predetermined interval for 24 hours. Complete sink condition was maintained by replacing the same volume of fresh dissolution medium after each sampling.

The samples were diluted to a suitable volume with phosphate buffer, and the absorbance was recorded at 273.5 nm using a UV spectrophotometer23. RESULTS AND DISCUSSION Physical appearance Pure aceclofenac used in the form of a faded white crystalline powder as stated in the physical identification results of the drug sample was identical to the reference standard. These results confirm the identity of aceclofenac. Determination of melting point The melting point value observed was 149ºC.

These values ??match the values ??mentioned in standard references (149-153ºC)22, confirming that the drugs used in this study were in their pure form. Solubility studies Aceclofenac has better solubility in phosphate buffer and does not have good solubility in distilled water and 0.1 N HCl, as presented in Table II. Table II. Solubility of aceclofenac Solvent _Solubility (mg/mL) _Remark _ _Distilled water _0.187 _practically insoluble _ _0.1N HCl _0.283 _practically insoluble _ _Phosphate buffer _0.841 _slightly soluble _ _ Compatibility study of drug and polymer (FTIR) The peaks at 3319 cm-1 and 3267 cm-1 in the FTIR spectrum of aceclofenac (Figure 2) are associated with OH hydrogen bonds.

This peak at 2970 cm-1 was due to the aromatic stretching of NH. The stick peak character near 2937 cm-1 may be due to the stretching of the CH from the CH groups. The peak at 1750 cm-1 indicates the presence of carboxylic acids in the compound. The peaks at 1589 cm-1, 1577 cm-1, and 1508 cm-1 indicate a stretch of the C = C ring. The overall functional group analysis is presented in Table III. Table III. FTIR spectrum of aceclofenac and its functional groups Peak (cm-1) _Remark _ _3319 _OH hydrogen bonding _ _3267 _OH hydrogen bonding _ _2970 _NH aromatic stretching _ _2937 _CH stretching _ _1750 _C=O stretching _ _1589 _C=C stretching _ _1577 _C=C stretching _ _1508 _C=C stretching _ _ Micromeritic properties The flow property of granules was estimated based on different micromeritic properties.

The bulk density and tapped density were determined using USP bulk density apparatus, and the results are represented in Table IV. The bulk density and tapped density were found to be almost similar, indicating similar flow properties. The differences in bulk density and tapped density were minimal, indicating that the change volume is significantly less even after 100 tapping30, which confirms uniform particle size range and reproducibility in drug. Hausner's ratio is related to inter-particle friction. Hausner's ratio is indirect measures of bulk density, size, and shape, surface area, moisture content, and cohesiveness of granules.

A higher Hausner's ratio and more fine particles indicate greater cohesion between particles, while a low range of Hausner's ratio indicates good flowability. The desirable value of Hausner's ratio is <1.25 for a good flow of materials. The Hausner's ratio of granules was determined and found to be in the range of 1.12±0.040 to 1.19±0.035. An increase in Hausner's ratio is due to an increase in granule size, and this might be due to increased void space between the particles31. It is well known that particle size and shape influence flowability. The fine particles (<100 mm) tend to be more cohesive and therefore less free-flowing, whereas larger denser particles tend to be free-flowing.

The rougher and more irregular the surface of the particles, the higher will be the angle of repose32. In the present study, the angle of repose increased from 26.78±0.600 to 30.60±0.566° as the particle size increased, indicating the decrease in flowability of granules33. This is also supported by the results of Hausner's ratio study. A high compressibility index is indicative of the tendency to form bridges between the particles. The smaller the compressibility index, the better the flow properties; for example, a value of 5 to 15 indicates excellent, 12 to 18 good, 19 to 21 fair and 22 to 35 poor, 36 to 40 very poor, and >40 extremely poor flow34.

The results show a compressibility index in the range of 10.93±0.150 to 14.76±0.462, which indicates excellent flow property.

/ Figure 2. FTIR spectrum of aceclofenac

Table IV. Results of micromeritic characterization of aceclofenac granules Formula _Bulk density (g/cm3) _Tapped density (g/cm3) _Compressibility index (%) _Hausner's ratio _Angle of repose (°) _ _F1 _0.438± 0.002 _0.503± 0.006 _12.4± 0.346 _1.14± 0.046 _30.60± 0.566 _ _F2 _0.429± 0.007 _0.479± 0.009 _12.65± 0.618 _1.12± 0.040 _30.00± 0.173 _ _F3 _0.477± 0.019 _0.560± 0.023 _14.76± 1.721 _1.17± 0.023 _28.03± 0.208 _ _F4 _0.491± 0.010 _0.551± 0.013 _10.93± 0.150 _1.12± 0.003 _28.30± 0.346 _ _F5 _0.416± 0.007 _0.471± 0.009 _11.74± 0.248 _1.13± 0.004 _27.24± 0.295 _ _F6 _0.412± 0.027 _0.479± 0.018 _14.0± 1.212 _1.16± 0.015 _26.78± 0.600 _ _F7 _0.477± 0.010 _0.556± 0.010 _14.20± 0.266 _1.166± 0.004 _27.77± 0.546 _ _F8 _0.466± 0.003 _0.541± 0.001 _14.05± 0.531 _1.623± 0.064 _27.29± 0.272 _ _F9 _0.478± 0.003 _0.561± 0.001 _14.76± 0.462 _1.19± 0.035 _27.34± 0.140 _ _ Post compression results The tablets were evaluated for weight variation, thickness, hardness, friability drug content, and in vitro drug release profiles.

Weight variation data indicates no significant difference in individual tablet weight from the average weight (500.333±0.577 to 502.33±0.577). Tablet hardness was observed within the range of 3.26±0.115 to 3.60±0.200 kg/cm2. A uniform thickness of the tablets was observed in the range of 3.23±0.004 to 3.28±0.008. The Friability of all the formulations was below 1%, indicating good mechanical strength of the tablets (Table V). From the in vitro drug release data, it was clear that the drug release was decreased with an increase in polymer concentration. The drug release was found to occur through a swelling process35.

Table VI was to find out the mechanism of drug release, and also to verify the fact that whether diffusion was Fickian or non-Fickian. The in vitro dissolution data of all the batches was plotted according to the Peppas' equation, in which cumulative log percentage of drug release was plotted against log time. From the kinetic data, it was evident that the drug release was found to follow Peppas' model for all the formulations, and the release was diffusion controlled.

The calculated slope values of Peppas' equations gave a value close to 1 but less than 1, which confirmed that the release mechanism of aceclofenac from the hollow beads was Fickian diffusion with swelling in both the media36. From Table VII, it was clear that all the formulations had 'n' values greater than 0.5 and less than 1, which confirms that the release mechanism of aceclofenac from the prepared matrix tablets in phosphate buffer was Fickian diffusion with swelling37. Table V. Post compression results of aceclofenac sustained release matrix tablets Formula _Weight (mg) _Thickness (mm) _Hardness (kg/cm2) _Friability (%) _Drug content (%) _ _F1 _501.33± 0.577 _3.23± 0.035 _3.53± 0.115 _0.31 _97.89 _ _F2 _501.67± 0.535 _3.26± 0.010 _3.60± 0.200 _0.48 _100.59 _ _F3 _500.67± 1.528 _3.25± 0.005 _3.46± 0.115 _0.64 _96.32 _ _F4 _502.33± 0.577 _3.27±

0.006 _3.40± 0.200 _0.71 _97.99 _ _F5 _500.68± 0.438 _3.28± 0.008 _3.26± 0.115 _0.33 _96.32 _ _F6 _501.33± 1.155 _3.25± 0.012 _3.33± 0.120 _0.47 _100.11 _ _F7 _501.23± 1.535 _3.24± 0.007 _3.33± 0.115 _0.63 _99.15 _ _F8 _502.33± 0.577 _3.27± 0.007 _3.40± 0.200 _0.68 _99.14 _ _F9 _500.33± 0.577 _3.23± 0.004 _3.50± 0.115 _0.65 _100.11 _ _ Table VI.

In vitro drug release of aceclofenac from sustained release matrix tablets in phosphate buffer Time (hours) _Formula _ _ _F1 _F2 _F3 _F4 _F5 _F6 _F7 _F8 _F9 _ _0 _0 _0 _0 _0 _0 _0 _0 _0 _0 _ _0.5 _2.57± 0.76 _2.05± 0.56 _1.91± 0.87 _1.77± 0.32 _2.44± 0.56 _1.86± 0.03 _1.82± 0.54 _1.44± 0.54 _1.5± 0.45 _ _1 _2.47± 0.54 _1.99± 0.87 _1.83± 0.77 _1.56± 0.43 _2.38± 0.65 _1.83± 0.09 _1.71± 0.54 _1.33± 0.76 _0.98± 0.33 _ _2 _2.69± 0.34 _2.11± 0.98 _1.88± 0.66 _1.69± 0.54 _2.53± 0.01 _1.94± 0.34 _1.86± 0.65 _1.8± 0.54 _1.28± 0.34 _ _4 _42.8± 0.12 _39.11± 0.45 _36.73± 0.87 _32.39± 0.65 _40.58± 0.08 _39.23± 0.87 _36.34± 0.65 _31.27± 0.67 _20.86± 0.43 _ _6 _51.34± 0.03 _51.46± 0.32 _52.69± 0.56 _46.88± 0.55 _53.07± 0.32 _52.5± 0.98 _51.73± 0.07 _46.35± 0.98 _29.56± 0.65 _ _8 _63.65± 0.09 _62.47± 0.22 _61.15± 0.67 _56.42± 0.43 _62.46± 0.43 _63.07± 0.67 _59.81± 0.09 _54.54± 0.97 _43.8± 0.66 _ _10 _78.26± 0.07 _74.12± 0.08 _70.38± 0.08 _66.73± 0.55 _76.54± 0.03 _74.04± 0.34 _68.85± 0.08 _63.26± 0.65 _51.16± 0.55 _ _12 _96.34± 0.94 _86.59± 0.65 _81.73± 0.76 _76.59± 0.76 _95.58± 0.32 _85.38± 0.45 _80.58± 0.07 _72.12± 0.09 _59.04± 0.06 _ _16 _- _100.34± 0.44 _89.6± 0.66 _86.31± 0.65 _- _100.38± 0.54 _87.88± 0.05 _82.19± 0.09 _70.77± 0.66 _ _20 _- _- _99.61± 0.32 _95.76± 0.76 _- _- _99.81± 0.04 _92.81± 0.87 _84.03± 0.07 _ _24 _- _- _- _100.19± 0.43 _- _- _- _99.8± 0.05 _99.04± 0.55 _ _ In this work, an attempt was made to formulate and evaluate sustained release matrix tablets of aceclofenac to maintain the plasma drug concentration constant for the whole day.

It also helps in decreasing the dosing frequency by which the patient compliance increases. Aceclofenac has a very short half-life (t½ 2-4 hours), so in conventional tablets, aceclofenac dosing frequency is more. Drugs with a short half-life cannot maintain the plasma drug concentration at the therapeutic levels for a more extended period38. Thus, to decrease the dosing frequency and increase patient compliance, sustained release matrix tablets were formulated. In the preformulation studies, aceclofenac was characterized based on its physicochemical properties by determining melting point, solubility, UV spectroscopy, and FTIR studies.

There were no physical changes after, and also no significant interaction of drug with polymers was observed in the UV and FTIR analysis after four weeks as the drug and polymers were compatible and thus were finalized to use in the formulation of sustained-release tablets29. Quality parameters such as tablet diameter, thickness, hardness, friability, and dissolution profile were evaluated. The best release profile was

obtained from tablets containing Guar gum matrix former without HPMC in an equivalent proportion to the drug (F8). The best-selected tablet formulation had friability 0.68%, hardness 3.40±0.200 kg/cm2, and 99.8±0.05 drug release after 24 hours of the dissolution study. Table VII.

Estimated values of diffusional exponent and correlation coefficient from the dissolution data of aceclofenac in phosphate buffer Formula _Zero order (r2) _First order (r2) _Higuchi's model (r2) _Peppas' model _ _ _ _ _ _r2 _n _ _F1 _0.9711 _0.9118 _0.9973 _0.9813 _0.612 _ _F2 _0.9709 _0.8666 _0.9964 _0.9674 _0.598 _ _F3 _0.9687 _0.8412 _0.9959 _0.9784 _0.632 _ _F4 _0.9770 _0.8204 _0.9957 _0.9809 _0.618 _ _F5 _0.9771 _0.8070 _0.9934 _0.9712 _0.545 _ _F6 _0.9718 _0.8296 _0.9950 _0.9778 _0.625 _ _F7 _0.9770 _0.8066 _0.9964 _0.9840 _0.559 _ _F8 _0.9696 _0.8079 _0.9947 _0.9824 _0.573 _ _F9 _0.9712 _0.8400 _0.9978 _0.9785 _0.632 _ _ CONCLUSION In this study, the prepared matrix aceclofenac tablet showed significant drug release property.

It maintains the constant concentration for a long time means that it increases the half-life and bioavailability of the drug.

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