FORMULATION DEVELOPMENT AND *IN-VITRO* EVALUATION OF MODIFIED FILM COATED DICLOFENAC POTASSIUM TABLETS

Sibt.ul.Hassnain Abbas
Albro Pharmaceuticals Private Limited, Lahore, **PAKISTAN**
Riphah Institute of Pharmaceutical Sciences.
Riphah International University, Lahore Campus, Lahore, **PAKISTAN**

ABSTRACT

Tablets is the most common drug delivery system used for oral route of administration and can be manufactured by various methods like wet granulation, dry granulation and direct compression. Direct compression is highly efficient, less laborious and increasingly becoming more popular than both dry granulation and wet granulation methods. Diclofenac potassium has excellent antipyretic, analgesic and anti-inflammatory properties. Diclofenac potassium is claimed to dissolve faster and hence absorbed faster than sodium salt. It is also indicated for the treatment of primary dysmenorrhea and mild to moderate pain. Diclofenac Potassium tablet had shown the problem of having D.T. on higher side with wet granulation method and also time and energy consuming along with this sugar coated tablets did not give the dissolution results upto the standards. To resolve these issues convert the wet granulation to direct compression method that will reduce the D.T. and sugar coating will be replaced with aqueous film coating that will give improved dissolution profile.

INTRODUCTION

Oral route for administration is the most commonly used route for drug administration. The most popular form for oral drug delivery is the tablets (Winfield A., 2004), which are one of the most convenient drug administration routes for the patients and they are usually easy to handle and identify (Winfield A., 2004, Lachman Liebermann H., 2009).

In recent years, more emphasis has been placed on dissolution testing within the pharmaceutical industry and correspondingly, by regulatory authorities. As a result FDA and WHO (FDA Center for Drug Evaluation and Research, 1997. & WHO Technical Report Series. Multisource (generic) pharmaceutical products: 2006. No: 937.) provide recommendations to compare dissolution profiles. A dissolution profile is defined as the measured fraction (or percentage) of the labelled amount of drug that is released from a dosage unit (tablet or capsule) at a number of predetermined time points when tested in a dissolution apparatus, such as the US Pharmacopeia (USP) I or II dissolution systems. The FDA suggest some acceptable approaches for establishing similarity of dissolution profiles, such as the model-independent and model-dependent approaches, although any approach would be considered once it had been justified.

Tablets are commonly manufactured by one of the following manufacturing processes: Direct compression, Wet granulation and Dry granulation methods. (Jones D., 2008) Direct compression is highly efficient, less laborious and increasingly becoming more popular than both compression granulation and wet granulation methods in the manufacturing of tablets. However, few drug powders can be manufactured by the direct compression method, while most drugs need the incorporation of other excipients in order to achieve satisfactory

properties such as strength, disintegration and dissolution times. One such excipient is the binding agent. (Ayorinde J, et al. 2011; 47(4): 845-854.)

Diclofenac potassium, an important non-steroidal anti-inflammatory drug (NSAID), was chosen in the present study due its poor compressibility. (Ayorinde J, et al. 2011; 47(4): 845-854.).

Diclofenac is commercially present as sodium and potassium salt in tablets for oral administration and as diethylamine for topical application. While extensive literature is available for sodium salt (O´Connor KM and O Corrigan. 222.2 (2001): 281-293 & Su SF., et al. 260.1 (2003) 39-46.), little has been reported on the potassium salt (Fini A., et al. 90.12 (2001): 2019-2057.).

Diclofenac potassium has excellent antipyretic, analgesic and anti-inflammatory properties. Diclofenac potassium is claimed to dissolve faster and hence absorbed faster than sodium salt. It is also indicated for the treatment of primary dysmenorrhea and mild to moderate pain (Chuasuwan B., et al. 98.4 (2009): 1206-1219.).

Diclofenac potassium is classified as a class II drug as per the biopharmaceutical classification system (BCS) (Chuasuwan B., et al. 98.4 (2009): 1206-1219.). The poor dissolution rate of water-insoluble drugs is still a major problem confronting the pharmaceutical industry. (Fini et al.1996: 231-238) studied the dissolution efficiency of diclofenac salts prepared using alkaline metals hydroxide or organic aliphatic bases.

Diclofenac Potassium tablet had shown the problem of having D.T. on higher side with Wet Granulation method and also time and energy consuming along with this when sugar coated did not give the dissolution results upto the standards. To resolve these issues convert the wet granulation to direct compression method that will reduce the D.T. and sugar coating will be replaced with aqueous film coating that with give improved dissolution profile.

AIMS AND OBJECTIVES

- To improve Dissolution
- To improve physicochemical properties of Diclofenac Potassium Tablet via direct compression
- To control drug release by modifying sugar coating with aqueous film coating
- To evaluate the effect of different process variables on synthesis and drug release profile

MATERIALS

The following materials will be used:

- Diclofenac Potassium (China)
- Spray dried Lactose (Germany)
- Maize Starch (Rafhan, Pakistan)
- Aerosil V200 (China)
- Magnesium Stearate (Pakistan)
- Primogel (Pakistan)
- Avicel M102 (India)
- R.O.Water
- Methocil E-5 (China)

- Tio_2 (Pakistan)
- Tween-80 (Pakistan)
- Lake color (Pakistan)
- PEG 6000 (Pakistan)

INSTRUMENTS

The following instruments will be used during the practical work.

- UV-Spectrophotometer (Hitachi, Japan)
- pH meter Digital weighing balance (WTW, Germany)
- Automatic dissolution apparatus USP (Pakistan)
- Sieves with different mesh numbers (Pakistan).
- Powder Mixer (Pakistan)
- Friabiliator (Curio International, Pakistan)
- ZP-17 tablet machine (China)
- Digital Hardness tester (Galvano Scientific, Pakistan)
- Coating Machine (Pakistan)
- FTIR (Roschanico, Australia)

PRE-FORMULATION STUDIES

Flow properties

Angle of repose of different formulations will be measured according to the fixed funnel standing cone method (Banker and Anderson, 1987).

$$\Theta = \tan^{-1} h\, r^{-1}$$

Where Θ is the repose angle, r is the radius and h is the height.

Compressibility index

(Ci) or carr index (Carr 1965) values of microparticles will be computed according to the following equation:

$$\text{Carr}\% = \frac{(\text{tapped density} - \text{fluff density})}{\text{tapped density}} \times 100$$

Hausner's Ratio

The Hausner ratio is used in a wide variety of industries as an indication of the flow ability of a powder. A Hausner ratio greater than **1.25** is considered to be an indication of poor flow ability. The Hausner ratio (H) is related to the Carr index (C), another indication of flow ability, by the formula. (Carr 1965)

$$Hausner\ \ Ratio = \left(\frac{\rho_{tapped}}{\rho_{bulk}} \right)$$

Assay of Diclofenac Potassium by UV:

Preparation of the Standard Solution:

Weigh accurately about 50mg of Diclofenac Potassium working standard and transfer quantitatively into a 100ml V/flask. Dissolve and dilute to 100ml with 0.1M NaOH. Dilute 2ml of the clear solution of the filtrate to 50ml into a 50ml volumetric flask with 0.1M NaOH.

Preparation of the Sample Solution:
Grind grain in a mortar and accurately weigh sample powder equivalent to 50mg of Diclofenac potassium. Quantitatively transfer the sample into a 100ml volumetric flask. Add about 60-70ml of 0.1M NaOH solution, shake for 5–10 minutes and dilute to volume with 0.1M NaOH. Filter, through Whatmann 42 filter paper discarding the first part of the filtrate (15–20ml) and dilute 2ml of the clear solution of filtrate to 50ml in another 50ml volumetric flask with 0.1M NaOH.

Procedure:
Measure the absorbance of the sample & standard solution at 276nm using 0.1M NaOH as blank.

Calculation:
The quantity of Diclofenac Potassium in mg/tablet and assay in %age can be calculated by the following formulae;

$$\text{mg of Diclofenac Pot. /tab} = \frac{A_{smp} \times W_{std} \times D_s \times W_{av} \times \text{Potency of std.}}{A_{std} \times D_{std} \times W_{smp} \times 100}$$

And

$$\%\text{age Assay} = \frac{A_s \times C_{std} \times \text{Potency of std.}}{A_{std} \times C_{smp}}$$

Where

A_s	:	Absorbance of sample solution
A_{std}	:	Absorbance of standard solution
C_{smp}	:	Concentration of sample solution
C_{std}	:	Concentration of standard solution
D_s	:	Dilution of sample
D_{st}	:	Dilution of standard
W_{st}	:	Weight of standard taken
W_s	:	Weight of sample taken
W_{av}	:	Average weight per tablet

Formulation Manufacturing
Preparation of formulations of Diclofenac Potassium using different polymers
To observe the effect of polymer on drug release rate, various formulations will be prepared by fixing the ratio of Diclofenac Potassium and by changing the polymers and methods. After mixing and sieving, the tablets containing equivalent weight of 75 mg of Diclofenac Potassium were compressed to tablets.

Preparation of Tablets
All the ingredients required for the preparation, i.e filler, polymers, drug and diluents will be weighed with the help of weighing balance. Then after weighing all the ingredients will be mixed together at the selected D:P ratio with excipients. Initially these will be mixed geometrically and then each powder mixture will be passed through a #30-mesh screen in order to achieve thorough mixing. Subsequently, magnesium stearate will be added and each resulting mixture will be passed again twice through the same mesh screen. After mixing each powder mixture will be directly compressed with help of tablets compressing machine and the hardness will be fixed 4-8 Kp.

Fourier Transform Infrared Spectroscopy (FTIR)
Drug-polymer interactions will be studied by FTIR spectroscopy. The spectra will be recorded for pure drug, polymer and drug-polymer matrix using FTIR. Samples will be applied in ATR (attenuated total reflectance) Zinc Selenide. The scanning range will be 4000-650 cm^{-1} and the resolution was 2 cm^{-1}. (B.P.2017)

Physico-chemical Parameters (Process variables)
Different physico-chemical parameters which will be considered are

- Different combination of Drug with same polymers and with different polymers
- Pressure applies during compression
- Speed of compression machine
- Coating with different polymers as with sugar coating and aqueous film coating
- Coating with different percentage of polymer selecting the best percentage for aqueous film coating

POST-FORMULATION STUDIES
Weight variation of Tablets
In order to determine the uniformity of tablet weight, twenty tablets of each formulation will be randomly collected and will be weighed using 'class A' weight balance and their percentage variation will be determined. Weight variation of tablets should be within the acceptance limits. (B.P 2017)

Hardness of Tablets
Hardness of tablets will be determined using automatic hardness tester. Ten tablets of each formulation will be used and the average hardness value will be calculated. Average hardness of all the formulations should be above 4-8Kp.(Albro Specs)

Friability of Tablets
The tablets of each formulation will be also subjected to friability testing employing friabiliator. The weight of twenty tablets prior to their placement in the chamber and at the end of the test will be recorded. The percentage weight loss will be then calculated. Triplicate measurements will be taken for each formulation. The acceptable limit of weight loss should not be more than 0.3 %. (B.P 2017)

Assay OF Diclofenac Potassium BY UV:
Preparation of the Standard Solution:
Weigh accurately about 50mg of Diclofenac Potassium working standard and transfer quantitatively into a 100ml V/flask. Dissolve and dilute to 100ml with 0.1M NaOH. Dilute 2ml of the clear solution of the filtrate to 50ml into a 50ml volumetric flask with 0.1M NaOH.

Preparation of the Sample Solution:
Grind 20 tablets in a mortar and accurately weigh sample powder equivalent to 50mg of Diclofenac potassium. Quantitatively transfer the sample into a 100ml volumetric flask. Add about 60-70ml of 0.1M NaOH solution, shake for 5–10 minutes and dilute to volume with 0.1M NaOH. Filter, through Whatman 42 filter paper discarding the first part of the filtrate (15–20ml) and dilute 2ml of the clear solution of filtrate to 50ml in another 50ml volumetric flask with 0.1M NaOH.

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And

$$\text{\%age Assay} = \frac{A_s \times C_{std} \times \text{Potency of std.}}{A_{std} \times C_{smp}}$$

Where

A_s	:	Absorbance of sample solution
A_{std}	:	Absorbance of standard solution
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C_{std}	:	Concentration of standard solution
D_s	:	Dilution of sample
D_{st}	:	Dilution of standard
W_{st}	:	Weight of standard taken
W_s	:	Weight of sample taken
W_{av}	:	Average weight per tablet

***In-Vitro* Drug Release**
***In Vitro* Drug Release Study**
In-vitro drug release of various formulations will be determined using the USP apparatus II. An equivalent amount of mix of different formulations containing 75 mg of Diclofenac Potassium will be placed in the bottom of dissolution flasks. Distilled water 900 ml maintained at 37.0 ± 0.5ºC will be added, Stirring speed will be set at 100 rpm. Sample of about 5 ml each will be collected at 0, 0.25, 0.5, 0.75, 1.0 hours. All the samples will be diluted up to 25ml and analyzed at 276 nm using a UV-spectrophotometer. Percentage drug releases at different sampling intervals will be calculated by taking the reading of pure drug solution (75mg Diclofenac Potassium in 900ml of water). All the tests will be run in triplicate and average will be taken. (B.P.2017)

Influence of pH on drug release rate of tablets
Tablets will be tested at different pH values i.e., pH 1.0 (0.1 N HCl) and pH 6.8 (phosphate buffer).

Effect of stirring speed on drug release rate of tablets
The effect of stirring speed on drug release rate will be evaluated on the test tablets. The different stirring speeds used will be 50, 100 and 150rpm.

Stability studies and batch reproducibility
In addition, test tablets will be divided into smaller portions and packed in an airtight amber glass bottles. The bottles will be kept at 8°C, 25°C and 40°C/75% RH. The samples of these tablets will be withdrawn after 1, 2 and 3 months and evaluated for stability in vitro release profile.

Application of kinetic models

The dissolution data will be fitted to commonly used model to determine release kinetic model i.e. Zero order, First order, Higuchi (Higuchi T ;1963), Hixson-Crowell (Hixson AW and Crowell JH. 1931) and Kosmeyer-Peppas (Korsmeyer RW et. al; 1983) models to determine the order and mechanism of drug release.

Equations of these models are given below:

Zero order kinetics: $F_t=K_0t$----------**Eq. 1**

First order kinetics: $\ln(1-F)=-K_1t$----------**Eq. 2**

Higuchi model: $F=K_Ht^{1/2}$---------- **Eq. 3**

Hixson Crowell: $(1-F)^{1/3}=1-K_{HC}t$----------**Eq. 4**

Korsmeyer–Peppas model $F=K_{KP}t^n$---------- **Eq. 5**

Where F is the fraction of drug released at time t. The k_0, k_1, k_H, k_{HC} and k_{kp} are the rate constants for zero-order, first order, Higuchi, Hixson-Crowell and Korsemeyer-Pappas model, respectively. Regression analysis will be performed to obtain the release rate constant and the values of coefficient of determination (r) will be compared.

In addition, the similarity factor f_2 (Moore et al 1996) will be used to compare the difference of dissolution profile of test tablets at stirring speed and the changing pH.

$$f_2=50\mathrm{Log}\left\{\left[1+1/n\sum_{t=1}^{n}(R_t-T_t)^2\right]^{-0.5}\times 100\right\}$$

Where n is the number of dissolution sample times and R_t and T_t are the individual percentages dissolved at each time point, for the reference and test dissolution profiles, respectively. f_2 value between 50 and 100 suggests that the data of two dissolution profiles are similar.

SIGNIFICANCE OF STUDY

The above study will be beneficial to the organization and consumer both as by direct compression, instead of wet granulation, the product exposure to atmospheric condition and other parameters as moisture, heat, grinding etc will be avoided and the quality of the product can be improved and also make it cost effective. And by modifying the sugar coating to aqueous film coating will improves the dissolution of the product or *In-Vitro* release which will make the product more efficacious also the D.T. of sugar coated tablet is not more than 01 hour whereas the D.T. for film coating is not more than 30 minutes which means that this study will be beneficial for organization and consumer.

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