IJBPAS, May, 2012, 1(4): 461-468

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

FORMULATION DEVELOPMENT OF SUSTAINED-RELEASE INDOMETHACIN MATRIX TABLETS

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ABSTRACT

Indomethacin is available as prescription and non-prescription medicine. The aim of this study was to prepare sustained released indomethacin matrix tablet using direct compression technique which is considered a cost effective and simple method of tablet manufacturing. In order to obtain the very best, optimized formulation, five different formulations of indomethacin were developed and evaluated in this study. Independent variables include, diluent(X1), polymer concentration(X2), and lubricant (X3). Dependent variables includes, weight variation (Y1) , thickness (Y2), diameter (Y3), Friability (Y4), Disintegration (Y5), and Dissolution (Y5). The result obtained was within the acceptable limit, i.e. conforming to official compendia. Interestingly, friability decreases with increasing polymer concentration while tablet crushing strength increases with increase polymer concentration. All the formulations did not disintegrate for well over five hours. Formulation A30 was selected as the best optimized indomethacin formulation.

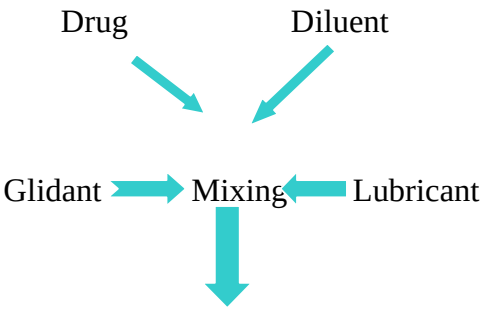
Keywords: Indomethacin, Direct Compression, Matrix Tablets, Non-Steroidal Anti-Inflammatory Agent

INTRODUCTION

Indomethacin is a commonly used Non-Steroidal anti-inflammatory agent (NSAID). NSAID are considered to be first line drug in the treatment of rheumatoid arthritis, osteoarthritis and spondylitis. The short biological half life (4.5hr) and hence

the frequency of administration make indomethacin a good candidate for sustained released.

Matrix tablets are made up of the drug and the polymer that control the release of the drug. The type, nature, and concentration of the polymer are vital to sustained release matrix tablets. There are three methods of tablet manufacturing with the choice depending on the dose, drugs physical properties such as compressibility and flow of the blend or granules [**1**]. Direct compression is a process by which tablets are compressed directly from the powder mixture of the drug and excipients without any preliminary treatment [**2**].



Production of pharmaceutical tablets by direct compression methods has increased steadily over the past ten years. Direct compression offers advantages over the other tablet manufacturing processes[3]. Direct compression is more economical, it also reduces the cycle time and it is straight forward in term of good manufacturing practice requirements. Thus there is an increasing focus by pharmaceutical companies recently on direct compression manufacturing process [**4, 5]**.

Also tablets produced by direct compression methods give lower microbial levels when compare to those prepare by wet granulation method [**6]**. The serious limitation of direct compression is low flowability and segregation [**7]**. The present study is to develop a sustained released indomethacin matrix tablet from locally developed ethylcellulose polymer.

MATERIALS AND METHODS

Indomethacin pure (Sigma-Aldrich Germany), Sawdust ethylcellulose (ABU Zaria) Kaolin (BDH), Magnesium Stearate (FMC Corporation USA), Talc (BDH).

Preparation of Indomethacin Matrix Tablet

The production of indomethacin matrix tablets follows the formulae in **Table 1** below;

Table 1: Various Formulations of Indomethacin Matrix Tablets

Materials	A30	A40	A50	A60
Indomethacin	75	75	75	75
SDEC	75	100	125	150
Talc	5	5	5	5
Mag St	0.5	0.5	0.5	0.5
Kaolin	94.5	69.5	44.5	19.5
Total	250	250	250	250

Various tablet ingredients were accurately weighed as in **Table 1**. These powders were then passed through 20 mesh sieve for each batch; indomethacin, Ethylcellulose (X1)

and kaolin (X2) were mixed for about 20 minutes with mortal and pestle. Finally magnesium stearate and Talc were added and mixed for another ten minutes. The blend was then compressed using single punch tablet machine (KORSCH, Erweka, Germany) fitted with 10 mm set of punch and die.

Optimization of Indomethacin Formulation

In other to obtain "best" or an "optimized formulation" five different formulations was generated using factorial design. Ethyl cellulose (X1) and kaolin (X2) were taken as independent formulation variables. While weight variations (Y1), thickness (Y2), diameter (Y3) hardness (Y4), friability (Y5), dissolution (Y6) were considered as dependent or response variables. The percentage compositions with the low and high levels of variables are shown in **Tables 2**.

Table 2: Variable selected for tablet optimization

	Variable	Low Level	High level
X1	**Qty SDEC**	**75**	**150**
X2	**Qty Kaolin**	**19.5**	**94.5**

Evaluation of Table Properties

After compression a number of different pharmacopoeia and non-pharmacopoeia physico-chemical tests were performed on all of the five formulations, which are as follow;

Weight Variation Test

The variation of the weight of individual tablets is a valid indication of the corresponding variation in the drug content **[8]**. The average tablet weight was determined by weighing 20 tablets individually using a digital analytical balance (type 163 mettler instruments Ag. Switzerland). The mean ±S.D. of each formulation is presented in **Table 4**.

Tablet thickness and Tablet diameter

The thickness of a tablet was determined by the amount of fill permitted to enter the die and the amount of pressure applied during compression **[9]**. 20 tablets were taken randomly for this purpose, the tablet thickness, and tablet diameter were determined individually with the aid of a vernier caliper. The Mean and ± standard deviation were calculated and presented accordingly.

Tablet Crushing Strength

20 tablets were taken randomly; the hardness was measured using Hardness Tester (Erweka Germany). The mean and ± S.D of 20 tablets of each formulation is shown in **Table 3**.

Friability Testing

20 tablets were taken randomly and placed on a sieve. Loose dust was removed with the aid of a soft brush. Tablet samples were weighed accurately and placed in Erweka tablet tester (Type TA3R, Erweka

Germany). After the given number of rotations (100 rotations) loose dust was removed from the tablets as before and the finally tablets weight determined. The lost in weight indicate the ability of the tablets to withstand stress of handling and transportation [**10]**.The percentage friability was determined by using following formula:

% friability =initial weight- final weight⁄ initial weight x 100

Disintegration Test

Sustained released matrix tablets are not expected to disintegrate like convectional tablets **[11, 12]**. Disintegration time was measured by using 6 tablets from each formulation, i.e. one tablet per disintegrating basket. Disintegration Apparatus was Erweka type ZT-2, Huesnstanm Germany.

Dissolution Test

Dissolution of indomethacin matrix tablets from was conducted according to the USP 27 NF 22, 28th edition (United state pharmacopoeia 2005). Selected rotation speed was 50 rpm, in 900ml of borate buffer solution pH 7.0 at 37± 0.5°C, 10ml of the dissolution medium was withdrawn at regular interval of 4hours, this was filter and absorbance of 1% w/v was taken using UV-VIS Spectrophotometer (Shimadu, Japan), equal volume of borate buffer kept at 37^{o}C was added to keep the volume of the medium constant. The indomethacin concentration of each sample (n-6) was determined at 241nm using following formula:

% Absorbance = Absorbance of sample / Absorbance of standard

RESULT AND DISCUSSIONS

All the tablets are spherical in shape and free from physical defects, the average tablet weights of all the formulations were constant indicating an excellent flow of the powder from the hopper to the die. The friability decrease from 0.6% for formulation A30, to 0.5% for formulation A60. Also interestingly, tablet crushing strength increase from5.5kgf formulation A30 to 6.2 KgF for formulation A60. These observation could be due to increase polymer concentration. Ethylcellulose could both act as drug release barrier and tablet binder. Increase in binder concentration could lead to increase in tablet crushing.

All tablets did not disintegrate for well over 5 hrs which is expected for sustained release matrix tablet. All other physicochemical tests were found to conform to the British Pharmacopeia.

Powder for compression must have good compressibility; problem in good compressibility could cause variation in the die filling and consequently variation in tablet weight, diameter and thickness **[13]**.

The purpose of formulation optimization is to select the possible formulation from pharmaceutical as well as customer point of view. In this study effects on response variables (Y) were observed by changing one variable (X) at a time. Optimization is considered as an efficient and economical method to understand the relationship between variables.

Formulation A30

This is the only formulation that shows acceptable dissolution profile, a well design sustained released matrix system should as a matter of principle release the active ingredient gradually and completely with the stipulated period of time. This is an essential formulation requirement in order to maintained constant therapeutic concentration of the active pharmaceutical ingredient in the body.

Formulation A40, A50 and A60

In these formulations we got between (19-28) % initial burst release of indomethacin in 4hrs and none of the formulations achieved more than 74% release of the active ingredient in 24hrs. This is not ideal as 100 % gradual released of the indomethacin from the polymer was expected in 24hrs, a condition which these formulations did not satisfied, even though the initial burst release of the active ingredient was achieve. These formulations have thus failed the formulation design and all the three formulations were rejected base on the dissolution release profile. Complete and total release of the active ingredient from the ethylcellulose polymer (in 24 hrs) will ensure a constant therapeutic concentration of indomethacin. Also dose dumping was not experience in any of the formulations. Dose dumping is a formulation problem that is associated with sustained release tablet technology, a situation in which all the unit dose of the active ingredient is release all at once, these if occurs can give rise to toxicity and unwanted side effects.

Table 3: The mean and ± S.D of 20 tablets of each formulation

Formulations	Friability	Avg. Wt.	Avg. TK	CS
A30	**0.6**	**250**	**2.89**	**5.5**
A40	**0.6**	**250**	**2.89**	**6.0**
A50	**0.5**	**250**	**2.89**	**6.2**
A60	**0.5**	**250**	**2.89**	**6.2**

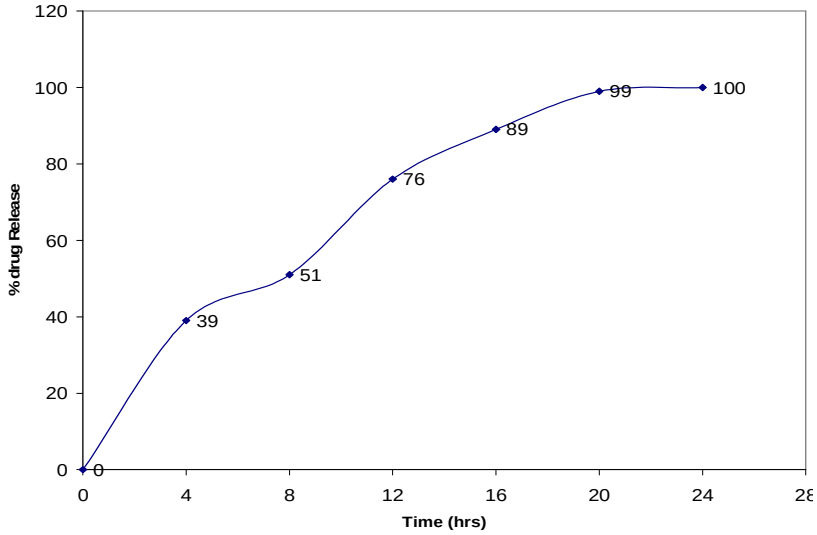


Figure 1: Dissolution Profile of Formulations A30

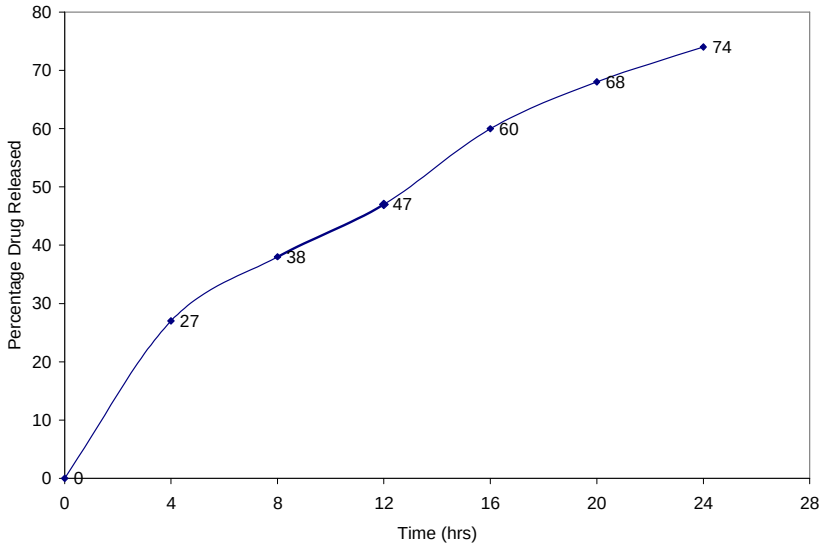


Figure 2: Dissolution Profile of formulation A40

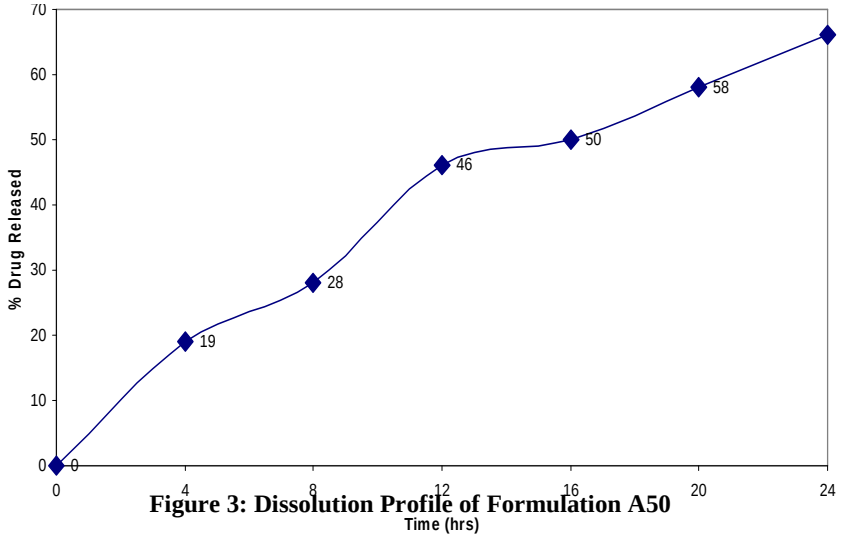


Figure 3: Dissolution Profile of Formulation A50

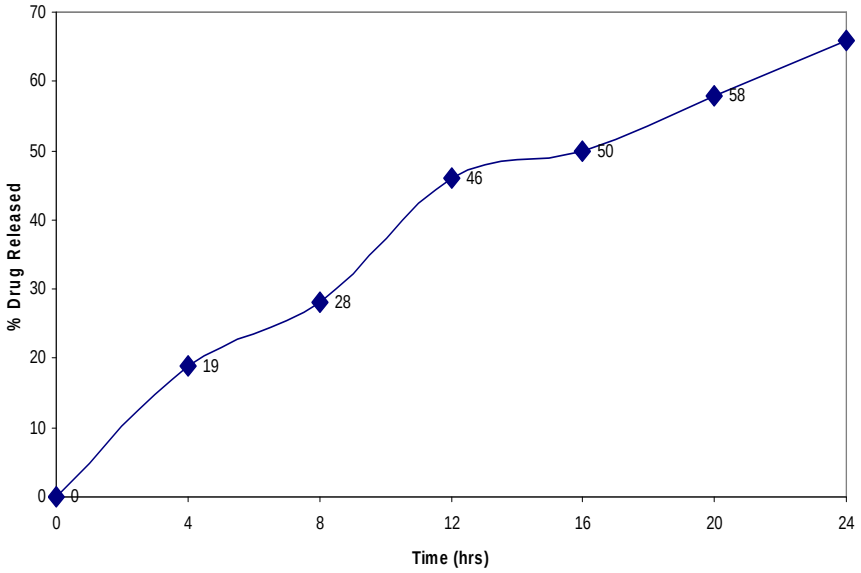


Figure 4: Dissolution Profile of Formulation A60

CONCLUSION

Base on research finding we came to the following conclusions. Direct compression method can be used alternatively for the development of sustained released matrix system. The suitability of locally processed

ethyl cellulose for sustaining the release of indomethacin for a period of 24 hrs at a polymer concentration not above 30% of the total weight of the tablet was demonstrated.

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