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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF IMDOMETHACIN BY WET GRANULATION METHOD

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ABSTRACT

The main aim of the study was to develop sustained release matrix tablet of Indomethacin by wet granulation technique. Indomethacin is a non- steroidal anti-inflammatory drug and COX inhibitor. By wet granulation method, all the ingredients were taken and passed through sieve no. 40 and granulated by passing through sieve no. 25, the matrix tablet were compressed by using 10 station Rimek mini press. The preparation was evaluated for micromeritics properties such as bulk density was achieved on an average 0.424 gm/ml, tapped density was 0.494 gm/ml, average Carrs's index 1.214, and angle of repose 28.136º. Followed by physicochemical properties i.e. hardness test 4.93 kg/cm^3, weight variation 199.44 mg, friability 0.256%. The percentage drug liberated was found between 83.02% to 98.19% due to the various concentration of HPMC K100M. The stability study, shows that percentage drug content determined periodically at a temperature of 40^{0}C at 75% RH evaluated at different time intervals, the control sample and test sample are kept at different storage condition at different RH. The granules show good flow properties and test performed are within standard limits. The stability study show that preparation was found to be stable. Drug release studied was carried out in 0.1N for 1.5 hours and till 12th hour in 7.4 pH Phosphate buffer. The release suggested that the formulations FA to FE showed a relationship as decrease in drug release as increase in concentration of HPMC K 100, where FA had the lowest concentration and FE having the highest concentration.

KEYWORDS: Indomethacin, Sustained release, Wet Granulation, HPMC K100, Gaur Gum.

INTRODUCTION

Indomethacin is a non-steroidal anti-inflammatory drug (1) (NSAID) commonly used as prescription medication. Its mechanism is by inhibiting the production of prostaglandin, endogenous signalling molecule. The clinical indication of Indomethacin includes Arthritic gout, Bursitis, Corneal Abrasion, Osteoarthritis.[1] Indomethacin actively participate in prostaglandin synthesis from arachidonic acid by inhibiting cyclo-oxygenase (COX) 1 and 2.[2] Clinically Indomethacin has various mode of action i.e.

1. Inhibits motility of poly morphonuclear leukocytes.[1]
2. Decreases cerebral blood flow.[3]

The sustained release matrix tablet of Indomethacin shows improved therapeutic action i.e. discharge of medication over increased time by administering a single dose. The design of matrix tablet holds many advantages over conventional dosage form like, improved patient compliance[4], decreased level of drug in systemic circulation. Indomethacin is insoluble in water[5] and sparingly soluble in alcohol as Indole derivative.[6]

Chemically Indomethacin is *1-(4-chlorobnzoyl)- 5- methoxy-2- methyl-1H- indole-3-acetic acid.*[7] Gaur gum is used in preparation of (indomethacin) matrix tablet which acts as thickening and stabilizing agent[8], gaur gum is selected because of its non-toxic nature and easy compression and swelling property. HPMC K100 is used as polymer because of its high purity and it has viscosity range of 75,000 to 140,000.

MATERIALS AND METHODS

Ingredients used in the Formulation Indomethacin Sustained Release

Indomethacin was provided by Theon Pharmaceuticals Pvt Ltd, Himachal Pradesh. The polymer HPMC K-100, Talcum powder Magnesium Stearate, Lactose were procured from Loba chemi pvt. Ltd, Mumbai. PVP K 30 from Sisco Research Laboratories Pvt Ltd, Mumbai. Isopropyl Alcohol was procured from Merck, Germany.

Preparation of Indomethacin Sustained Release Matrix Tablet

Sustained release matrix tablet of Indomethacin was carried out by wet granulation technique.[9] All the ingredients were passed through sieve no. 40 in increasing order of weight. Indomethacin, HPMC, Lactose and Guar gum was blended to form a wet mass using PVP 30 and granulating fluid i.e. Isopropyl Alcohol. This was granulated by passing through mesh no. 25. Granules are allowed to dry at room temperature.[10] Lubricating agent

Magnesium Stearate and Talc was employed.[11] The sustained release matrix tablet was compressed by means of 10 station Rimek Mini Press 1 (Model No: - 0200196).[12,13] The composition of formulation is given in table no. 1.

Table No. 1: Composition of formulations.

Composition	**FA** (mg)	**FB** (mg)	**FC** (mg)	**FD** (mg)	**FE** (mg)
Indomethacin	40	40	40	40	40
HPMC K 100M	20	30	40	50	60
Lactose	107	97	87	77	67
Guar Gum	20	20	20	20	20
Magnesium Stearate	4	4	4	4	4
Talc	6	6	6	6	6
PVP K 30	3	3	3	3	3
Isopropyl Alcohol	q. s	q. s	q. s	q. s	q. s
Total	200	200	200	200	200

1. Micromeritic Properties

Bulk Density

Bulk density apparatus (Electrolab Model No. 1020) was employed to study bulk density and tapped density. In a graduated cylinder the samples to be measured were added. Bulk and Tap density were calculated using below formula.[14]

$$Bulk\ Density = \frac{Mass\ of\ poder\ obtained}{Volume\ occupied\ by\ it}$$

$$Tapped\ Desity = \frac{Mass\ of\ Powder\ obtained}{Tapped\ Volume}$$

Carr's Index

Compressibility index established using bulk density and tap density values of a fixed sample weight. It is calculated as.[14]

$$Carr'sIndex = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density}$$

Angle of Repose

By using fixed funnel method the flow properties of powder is calculated to measure angle of repose. The powder is added in a funnel and length of the funnel is adjusted like it just it just touches powder mass. It is assessed by means of mathematical method (1).

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where, r = radius of mass base

θ = angle of repose

h = height of powder mass.

2. Physicochemical Properties

Hardness Test

By using Hardness test apparatus, the rigidity of tablet were carried out by placing tablet between the apparatus where, screw knob is slowly moved forward till tablet breaks. And readings are measured accordingly.[15,16] Hardness test is to measure the resistance of tablet during transportation and storage condition. It is measured in kg/cm^3.

Weight variation

Twenty were randomly selected and weighed in a Digital weighing balance, Manufactured by Shimadzu (Model No. BL 220H), weight of individual tablet was taken, then the percentage deviation was calculated.[14,17]

$$\%Deviation = \frac{[(Average\ weight) - (Weight\ of\ Tablet)]}{Average\ weight} * 100$$

Friability test

By using Electrolab friabilator (Model No. EF 2 USP), twenty tablets were taken and placed in it and 25 rpm is set for 4 min, after 100 revolution, the tablets were acquired out of friabilator and ratio of friability was determined.[15,18]

$$\%Friability = \frac{[(Initial\ weight) - (Final\ weight)]}{Initial\ weight} * 100$$

Drug Content

The matrix tablets of Indomethacin were analysed for their drug content using 20 tablets. Mass of the powder equivalent to 10 mg of Indomethacin was weighed and dissolved in ethanol and diluted further to estimate drug concentration using Shimadzu UV-Spectrophotometer UV 1800 at 320 nm.[19] It is given as.[20,21]

$$Drug\ Content\ (\%) = \frac{Weight\ of\ drug}{Weight\ of\ Tablet} * 100$$

Invitro drug release studies

The drug discharge of Indomethacin was accomplished by means of USP apparatus type II at 50 rpm (Manufactured by Electro lab, Model No. TDT 08L). The dissolution experiment was

accomplished using 900 ml of 0.1 N HCl at 37 ± 0.5 °C. A tablet was added in dissolution media. Test was conducted for a period of 3 hours. The drug release was calculated by taking 10ml sample (which was replaced with fresh medium) every one-hour interval. Later the dissolution was continued by using phosphate buffer pH 7.4 as dissolution media up to 9 hours. The sample withdrawn was calculated for absorbance at 320 nm using UV spectrophotometer.[22]

Drug Excipient Compatibility Studies

FTIR Spectroscopy

The study was performed Using Shimadzu FTIR- 8400S Spectrophotometer. The Spectrum of pure Drug, Drug+ HPMC K100 and Drug+ PVP K30 was obtained.

Stability testing of Indomethacin Sustained release matrix tablet formulation.

The formulated Indomethacin matrix tablet were placed in stability chambers Thermolab Humidity Chamber having Model No. as FUJI Electric PXR-4 at different storage conditions. The control samples were kept at 2-8^{o} C and test samples were kept at room temperature and at 40^{o} C/ 75% RH. The percentage drug content in tablet was determined and periodically i.e. 15 days and one month the samples were taken and analysed.[23,24]

Drug Release Kinetics

The release kinetics studies were performed by BCP software. Various plots like zero order, first order, Higuchi plot and Peppas plot was obtained.

RESULTS AND DISCUSSION

From Table 2, the granules were evaluated for the various flow properties. Range of bulk density was observed from 0.38 to 0.48 gm/cm^3 was obtained as a result of tap density value of 27.08 to 30.86 given as angle of repose. Carr's indices found out to be from 1.20 to 1.23. Thus, all the values were indicated that the granules have a good free flowing property.

Table No. 2: Micromeritic Properties

Evaluation Parameters	FA	FB	FC	FD	FE
Bulk Density (gm/ml±SD)	0.48 ± 0.14	0.44 ± 0.16	0.41 ± 0.18	0.38 ± 0.22	0.41 ± 0.29
Tapped Density (gm/ml±SD)	0.54±0.84	0.49±0.18	0.47±0.34	0.45±0.43	0.52±0.84
Carr's Index (±SD)	1.20 ± 0.76	1.21 ± 0.78	1.22 ± 0.80	1.21 ± 0.75	1.23 ± 0.68
Angle of Repose (degree±SD)	30.86 ± 0.84	27.41 ± 0.85	27.08 ± 0.61	27.62 ± 1.02	27.71 ± 1.07

All the formulated Matrix tablet showed good elegance in appearance. The hardness of all formulation was within the range of 4.90 to 4.96 kg/ cm^2, signifying reasonable mechanical strength. The loss in particle weight due to friability is not more than 1% indicating good mechanical strength of tablet, the weight variation was within the range of 199.5 ± 4.3%, drug content was observed to be in the range of 98.05±0.0458 which complies with pharmaceutical specification. (Table No. 3).

Table No. 3: Physicochemical Properties.

Evaluation Parameters	FA	FB	FC	FD	FE
Hardness (kg/cm^3±SD)	4.90 ± 0.10	4.93 ± 0.30	4.96 ±0.32	4.95 ± 0.27	4.91 ± 0.28
Weight variation (mg±SD)	199.3 ± 3.5	199.6 ± 3.7	199.4 ± 4.3	199.8 ± 3.6	199.1 ± 4.9
Friability (%±SD)	0.40 ± 0.08	0.29 ± 0.03	0.21 ± 0.09	0.18 ±0.02	0.20±0.10
Drug content (% ± SD)	98.85 ± 0.0664	99.51 ± 0.0721	97.60 ± 0.0321	98.14±0.0264	98.42 ± 0.0529

Table No. 4: Drug Release Studies in 0.1N HCl.

Time (h)	FA(%)± SD	FB(%) ± SD	FC(%) ± SD	FD(%) ± SD	FE(%) ± SD
0.5	3.08 ±0.36	2.05 ±0.30	2.31 ±0.26	2.05 ±0.38	1.80 ±0.33
1	8.26 ±0.72	5.42 ±0.36	4.39 ±0.36	3.36 ±0.37	4.90 ±0.73
1.5	11.79 ±0.55	8.80 ±0.37	9.30 ±1.08	7.23 ±0.73	8.15 ±0.92

Table No. 5: Drug release studies in Phosphate buffer pH 7.4.

Time (h)	FA (%) ± SD	FB (%) ± SD	FC (%) ± SD	FD (%) ± SD	FE (%) ± SD
2	15.81 ±0.73	11.54 ±0.55	14.88 ±1.28	11.13 ±0.75	10.12 ±0.37
3	29.38 ±1.20	25.74 ±0.97	25.78 ±1.46	19.59 ±0.95	20.94 ±0.97
4	42.77 ±0.73	38.81 ±0.97	38.13 ±1.40	33.97 ±0.95	33.99 ±0.94
5	54.67 ±0.47	49.86 ±0.95	49.00 ±1.22	43.33 ±0.47	43.33 ±0.97
6	64.00 ±0.97	58.33 ±0.73	56.10 ±0.98	52.63 ±0.96	49.90 ±0.47
7	74.33 ±1.46	68.64 ±0.73	68.11 ±1.46	64.15 ±1.21	60.37 ±0.72
8	84.16 ±1.22	75.91 ±0.72	75.56 ±0.74	71.77 ±0.73	67.81 ±0.92
9	90.05 ±1.22	83.83 ±0.71	81.95 ±0.97	76.11 ±0.47	71.81 ±1.21
10	94.03 ±0.98	87.49 ±0.49	86.79 ±0.97	80.59 ±0.96	76.97 ±1.22
11	96.29 ±0.73	90.60 ±0.97	88.71 ±0.73	82.17 ±0.73	80.60 ±1.94
12	98.19 ±0.49	89.78 ±1.21	89.59 ±0.71	88.12 ±0.74	87.98 ±1.47

From the above data (table no. 4 and 5) the percentage release of all formulation was found that the drug release gradually decreases from FA to FE batch due to increase in HPMC K100 as shown in figure no. 1.

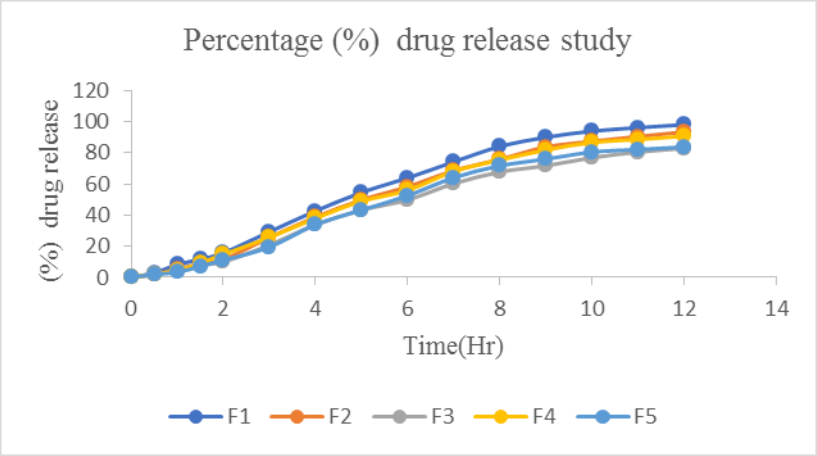

Figure No. 1: Comparison graph for Percentage (%) drug release.

FTIR spectra (shown in figure no. 2) there was no interaction of the drug with other excipients.

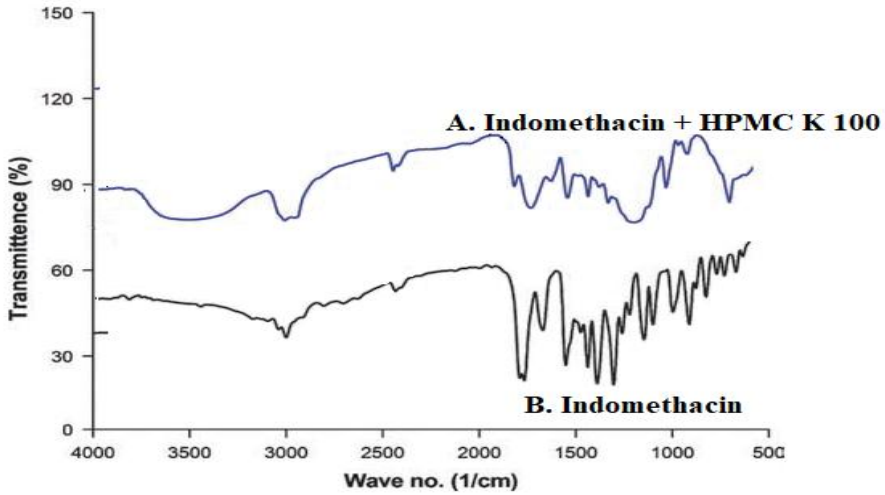

Figure No. 2: Fourier transform infrared spectroscopy (FTIR) of (A) FTIR spectra of indomethacin, (B) FTIR spectra of HPMC K 100 + Indomethacin.

Table 5: Stability data of Indomethacin Matrix tablet formulation.

Storage conditions	Percentage drug content at various time intervals		
	Day 0	Day 15	Day 30
Control (2-8^{o}C)	98.12±0.34	98.20±0.22	97.73±0.46
Room temp. (25^{o}C)	98.32±0.23	97.71±0.40	97.51±0.24
40^{o}C	98.27±0.31	97.88±0.25	97.18±0.48

According to table no.5, the formulation was said to be stable even after 30 days as the drug content was found to be in the acceptance range of 95% to 105%.

Release kinetics studies showed that the matrix tablet followed Zero order and then First order kinetics. It was more inclined to Higuchi plot. (figure no. 3).

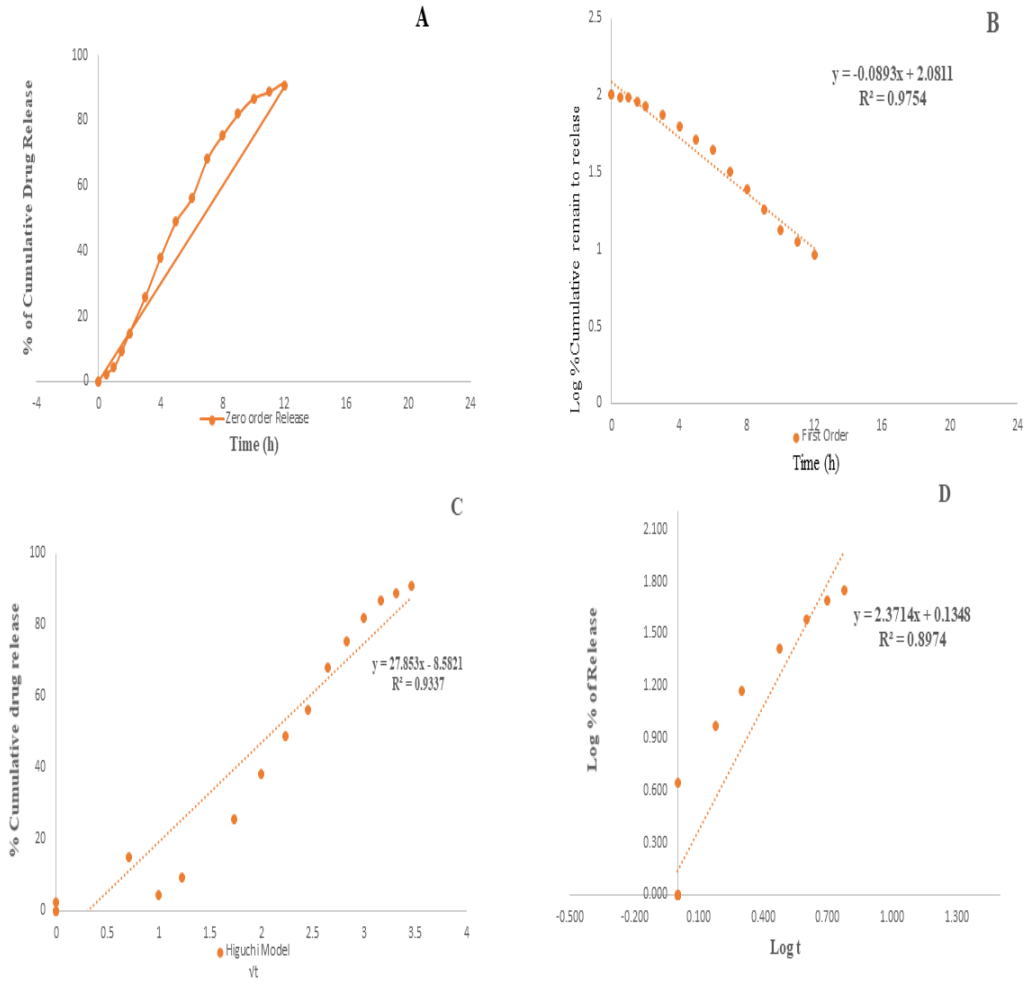

Figure 3(A): Zero Order Kinetics Plot, Figure No. 3(B) First Order Kinetics Plot, Figure No. 3(C) Higuchi Plot, Figure No. 3(D) Peppas Plot.

CONCLUSION

The results of Indomethacin tablet prepared, the granules of Indomethacin show decent flow assets, tablet calculation tests are within the suitable bounds and stability studies revelled that all the formulation were found to be stable. Thus, the results of the above study clearly indicate that Indomethacin may be formulated as sustained release tablet using HPMC K100 as polymer by wet granulation method, which will provide release of drug at predetermined rate. Of the five formulations, FA formulation containing a lower concentration of HPMC K 100 was termed to have the maximum drug release of 98.19 ±0.49 at 12th hour when tested in pH 7.4 Phosphate buffer.

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