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FORMULATION AND DEVELOPMENT OF INDOMETHACIN SUSTAINED RELEASE TABLETS

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ABSTRACT: The present study was aimed to formulation and development of indomethacin sustained release tablets by wet granulation method. The main objective of this work is decrease the dosage frequency, to decrease dose dumping, increase the patient compliance and to enhance the desired activity by adopting the wet granulation technique. In this study, excipients are selected in four different concentrations (F-1, F-2, F-3, and F-4) and formulated by wet granulation method. Then all four formulations are evaluated. By observing the dissolution profile of trials, trial-4 (formulation-4) was better formulation of all the trails. In trial-4 indomethacin was formulated as sustained release tablets by using ethyl cellulose and HPMC k-100. And that having good dissolution profile for a controlled period of time which shown 83.4% at end of 12th hour.

Keywords: Indomethacin, Ethyl cellulose and HPMC k-100

INTRODUCTION

Conventional dosage forms include solutions, suspensions, capsules, tablets, emulsions, ointments and suppositories. These dosage forms can be considered to release their active ingredients into an absorption pool immediately[1]. To overcome the potential problems associated with conventional drug therapy modified release/ non-immediate release delivery systems are developed and may be divided into categories like delayed release, sustained release, controlled release, prolonged release and receptor release[2].

In the case of new drug delivery systems, which are based on control of programmed drug delivery methods in the vicinity of target tissue, this undeniable fluctuation of drug levels (concentration) between toxic level and sub-therapeutic level can be greatly reduced. This controlled drug therapy offers a method for which therapeutic action is enhanced and the dangerous toxic level eliminated[3].

The scientific frame work required for development of a successful oral sustained release dosage form consists, of an understanding of three aspects of the system, namely,

(1) Physicochemical factors influencing oral sustained release dosage form design[6];

- Aqueous solubility
- Partition coefficient
- Drug stability
- Protein binding
- Molecular size and Diffusivity
- Dose size

(2) Biological factors influencing oral sustained release dosage form design[4];

- Absorption
- Distribution
- Metabolism
- Elimination and Biological half life[5]
- Side effect and safety consideration
- Plasma concentration response relationship

(3) Dosage form characteristics

- Dissolution controlled systems[7]
- Stagnant-layer control[9]
- Encapsulation dissolution control[10]
- Diffusional system[11]
- Matrix devices[8]

MATERIALS AND METHOD

Indomethacin (Shijiazhuang Pharma), Lactose (Hilmar chemicals), Starch (riddhi siddhi gluco boils ltd.), Ethyl cellulose (Zhejiang zhongbao imp & exp corp. ltd.), Methylene chloride (Gaja lakshmi dyes &

chemicals), Hydroxyl propyl methyl cellulose k-100M (Samsung chemicals), Talc (Mehta chemicals), Magnesium stearate (prachin chemicals).

Tablet punching machine 8 station (cadmach), Hardness tester (Tab-machines), Vernier calipers (Mitutoyo), Friability tester (Electro lab), Weighing balance (Shimadzu), Sonicator (Power sonic), pH meter (Susima), Dissolution tester USP (Electro lab), UV spectrophotometer (Shimadzu).

Anhydrous disodium hydrogen phosphate, Potassium dihydrogen phosphate, Methanol, DM water.

Method:

In Preformulation studies we have done angle of repose, bulk density, melting point, calculation of the sustained dose. Then formulation of indomethacin sustain release tablets was done by wet granulation method, we have done four trails in different concentration (F-1, F-2, F-3, F-4) of excipients as follows,

Table-1: Formulation of Indomethacin SR tablets by wet granulation method (Batch size -1000)

S. no	Ingredients	F1 (mgs)	F2 (mgs)	F3 (mgs)	F4 (mgs)
1	Indomethacin	75	75	75	75
2	Lactose	20	10	15	12
3	Starch	15	5	10	10
4	Ethyl cellulose N-7	7	26	18	20
5	Methylene chloride (ml)	40	50	50	60
6	HPMC-K-100	10	10	10	10
7	Talc	2	2	2	2
8	Magnesium stearate	2	2	2	2

In evaluation of indomethacin sustained release tablets we have done weight variation test, Thickness test, Hardness test, Friability test, Assay, Dissolution, Drug release kinetics.

RESULT AND DISCUSSION

A. Preformulation studies

1. Angle of repose: It is determined by fixed funnel method. The results where showed below.

Table-2: Determination of angle of repose

Formulation	Angle of repose
Indomethacin (pure drug)	30º45’
F1	26º22’
F2	25º27’
F3	24º15’
F4	22º21’

2. Bulk Density:

Bulk density was determined by cylinder method .The results where

Table-3: Determination bulk density

Formulation	Bulk density (gm/cc)
Indomethacin (pure drug)	0.426
F1	0.488
F2	0.551
F3	0.561
F4	0.589

3. Melting point:
Melting point was determined by capillary method the results were shown below,

Table-4: Determination of melting point

Material	Melting point
Indomethacin	158ºC

B. Evaluation of indomethacin sustained release tablets:

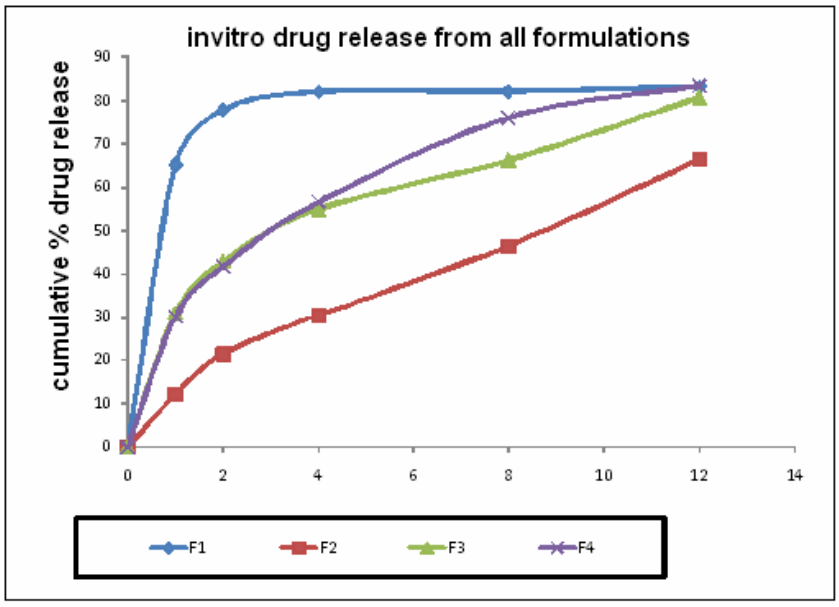
Table-5: Evaluation of physical properties of indomethacin SR tablets

Trial Batches	Average thickness(mm)	Average hardness(kg/cm²)	Friability (%)	Assay (%)	Average weight (mg)	Weight variation (mg) ±5%
F1	2.78	3.6	0.9	98.50	131.2	128.85-136.88
F2	2.80	3.5	0.1	99.19	130.9	124.64-137.42
F3	2.84	3.7	0.18	97.85	132.4	129.45-137.45
F4	2.80	3.5	0.09	99.85	131.04	130.44-136.55

Table-6: In-vitro dissolution studies for all formulations

Dissolution Medium	Time (in hours)	Cumulative % drug release			
		F1	F2	F3	F4
0.1M Hydrochloric acid	0-45 minutes	4.85	4.90	5.01	4.89
1 volume of pH 7.2 phosphate buffer and 4 volumes of water	1	65.15	12.12	30.86	30.11
	2	77.78	21.37	43.07	41.84
	4	82.01	30.46	55.03	56.64
	8	82.09	46.57	66.25	76.02
	12	83.19	66.39	80.69	83.34

Figure-1: In vitro drug release for all formulations



DISCUSSION

The present study was focused to formulate and develop indomethacin sustained release tablets. Preformulation studies were done .The angle of response and bulk density shows that the flow was well .The melting point shows that the indomethacin was pure. Formulations of indomethacin sustained release tablets were prepared as per wet granulation method.

The physical attributes of the tablet were found to be satisfactory .Typical tablet detects, such as capping, chipping & picking were not observed. Results for other physical evaluation were also found to be within an acceptable range. The assay percentages of all trials were found to be 98.5% to 99.85% (90% to 110%).

The dissolution results of all trials of indomethacin sustained release tablets were showed in table-

The formulated product of all the trials shows less release (<5%) in acid medium (0.1m hydrochloric acid) up to 45 minutes. The release rate was continued until the 12 hour mark. Hence, a sustained release pattern was observed in F-4 formulation throughout the 12 hour dissolution study.

CONCLUSION

From the above study it was concluded that indomethacin was formulated as sustained release tablets by using ethyl cellulose and HPMC K-100. It has shown constant release for 12 hours.

By observing dissolution profile of trials, we can conclude trial-4 was better formulation of all the trials, we can conclude that trial-4 was having good dissolution profile for a controlled period of time which shows 83.34% at end of 12^{th} hour.

As the drug release kinetics shows good result for the F-4, indomethacin can be used for better patient compliance. Decreasing the dose frequency of indomethacin increases patient compliance; patients prefer to take the drug once daily.

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