International Journal of Farmacia (IJF)

IJF |Vol.10 | Issue 2 | Apr - June -2024

www.ijfjournal.com

DOI : https://doi.org/10.61096/ijf.v10.iss2.2024.1-10

ISSN: 2231-3656

Research

Preparation And In Vitro Characterisation Of Indomethacin Sustained Release Tablets

Devendra Patil*[1], Ch. Sunitha[1], L. Harikiran[1]

Department Of Pharmaceutics, Princeton College Of Pharmacy In Narapally, Ghatkesar, Telangana

*Author for Correspondence: Devendra Patil
Email: surapharmalabs@gmail.com

Published on:19 April 2024

Published by:
DrSriram Publications

Abstract

The aim of the present study was to develop sustained release formulation of Indomethacin to maintain constant therapeutic levels of the drug for over 24hrs. By using different ratios of synthetic polymers like Methyl cellulose, HPMC K4 M, Hydroxyethyl cellulose (HEC). All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F8) showed better and desired drug release pattern i.e., 99.27% in 24 hours. It contains the Hydroxyethyl cellulose 1:1 ratio as sustained release material. It followed Kors mayer peppas release kinetics mechanism.

Keywords: Indomethacin Sustained release system, Methyl cellulose, HPMC K4 M, HEC.

INTRODUCTION

A drug delivery system (DDS) is defined as for formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time and place of release of the drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. The term therapeutic substance also applies to an agent. Sustained release tablets are commonly take only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect . the advantage of administering a single close of a drug that is released over an extended period of time to maintain a near – constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[5,6] .

The first sustained release tablets were made by Howard press in New Jersy in the early 1950's.The first tablets release under his process patent were called 'Nitro Glvn' and made under License by Key Corp.in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ[7,8].

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the Preparation of extended release formulations.

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged affective dose.

The above factors need serious review prior design.

Introduction of matrix tablet as sustained release (SR) has give a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery system. Matrix systems are widely used for the purpose of sustained release. It is the release system. which prolongs and controls the release of the drug that is dissolved or dispersed[9].

In fact, a matrix is defined as well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective connection can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

1.1 Rationale for extended release dosage forms:

Some drugs are inherently long lasting and require only one-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic result. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up does, and noncompliance with the regimen. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys(troughs) associated with the taking of each dose. However, When does are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If does are missed, periods of sub therapeutic drug blood levels or those below the minimum effective contraction may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect.

MATERIALS

Indomethacin-Procured From Ranbaxy Laboratories Ltd., New Delhi.Provided by SURA LABS, Dilsukhnagar, Hyderabad, Methyl Cellulose-Merck specialities Pvt Ltd, Mumbai, India, HPMC K4 M-Merck specialities Pvt Ltd, Mumbai, India, HEC-Merck specialities Pvt Ltd, Mumbai, India, PVP-Merck specialities Pvt Ltd, Mumbai, India, Aerosil-Merck specialities Pvt Ltd, Mumbai, India,Sodium Stearyl Fumerate-Merck specialities Pvt Ltd, Mumbai, India, Mannitol-Merck specialities Pvt Ltd, Mumbai, India

METHODOLOGY

Analytical method development

a) Determination of absorption maxima

100mg of Indomethacin pure drug was dissolved in 15 ml of Methanol and make up to 1000ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with 100ml by using 0.1N HCL (stock solution

-2 i.e 100µg/ml). From this 10 ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200-400nm.

b) Preparation calibration curve

100mg of Indomethacin pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (Stock solution-1). 10ml of above solution was taken and male up with 100ml by using 0.1N HCL (Stock solution-2 i.e 100µ/ml). From this take 1,2,3,4 and 5ml of solution and make up to 10 ml 0.1N HCL to obtain 10, 20, 30, 40, and 50 µg/ml of Indomethacin per ml of solution. The absorbance of the above dilutions was measured at 318 nm by using UV- Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis Which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) Which determined by least-square linear regression analysis. The above was procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique.

Formulation development of Sustained release Tablets

All the formulations were prepared by Direct Compression Method. The compositions of different formulations are given in the Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Indomethacin.

Procedure

1) Indomethacin and all other ingredients except sodium stearyl fumerate and Aerosil were individually passed through sieve no ≠ 40.
2) Indomethacin, Mannitol, and polymer mix thoroughly than add the binder solution mix properly up to 15 min.
3) Dry the above mixture at 65-70ºC by using dryer
4) After completion of drying the mixture is passed through sieve no ≠ 22.
5) The powder mixture was lubricated with sodium stearyl fumerate and Aerosil.
6) Finally go for compression.

Table 1: Formulation of Sustained release tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Indomethacin	50	50	50	50	50	50	50	50	50
Methyl Cellulose	25	50	75	-	-	-	-	-	-
HPMC K4 M	-	-	-	-	25	50	75	-	-
HEC	-	-	-	-	-	-	25	50	75
PVPK-30	5	5	5	5	5	5	5	5	5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium stearyl fumerate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mannitol	115	90	65	115	90	65	115	90	65
Total Wt	200	200	200	200	200	200	200	200	200

RESULTS AND DISCUSSION

The present work was designed to develop sustained tablets of Indomethacin using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Standard graph of Indomethacin in 0.1N HCL

The scanning of the 10 µg/ml solution of Indomethacinin the ultraviolet range (200-400nm) against 0.1 N HCL the maximum peak observed at λ_{max} as 318 nm. The standard concentration of Indomethacin (10-50 µg/ml) was prepared in 0.1N HCL showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

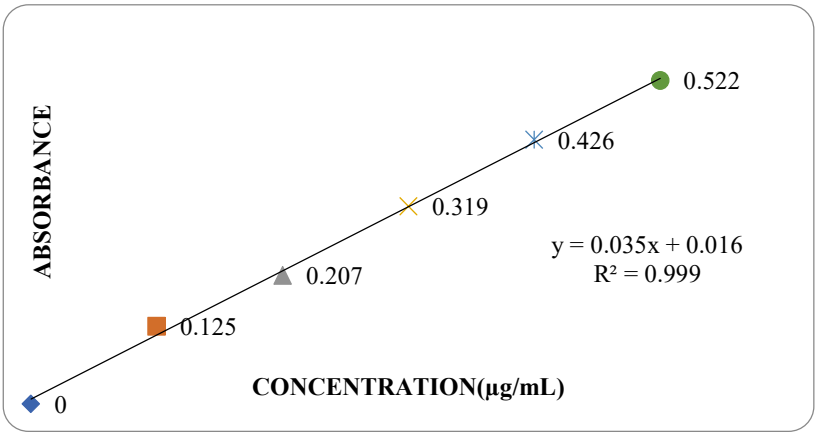

Fig 1: Calibration curve of Indomethacinin 0.1N HC1 at 318 nm

Standard Curve of Indomethacinin Phosphate buffer pH 6.8

The scanning of the 10 µg/ml solution of Indomethacinin the ultraviolet range (200-400nm) against 6.8 pH phosphate the maximum peak observed at the λ_{max} as 318 nm. The standard concentrations of Indomethacin (10-50 µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

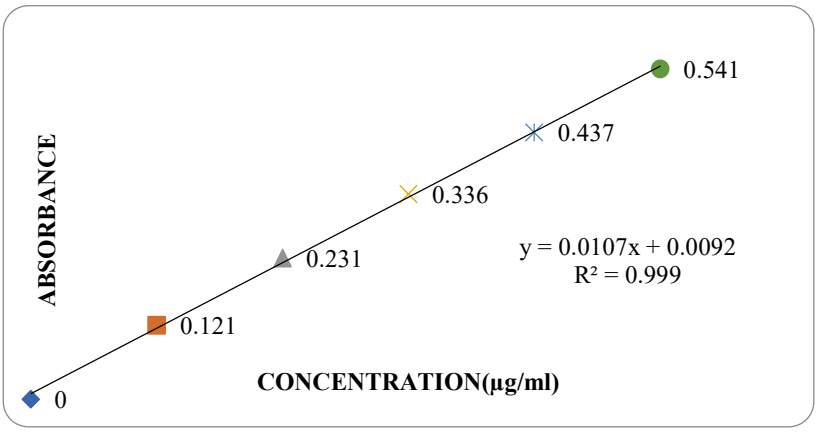

Fig 2: Calibration of Indomethacinin Phosphate buffer pH 6.8

Drug and Excipient Compatibility Studies

FTIR study

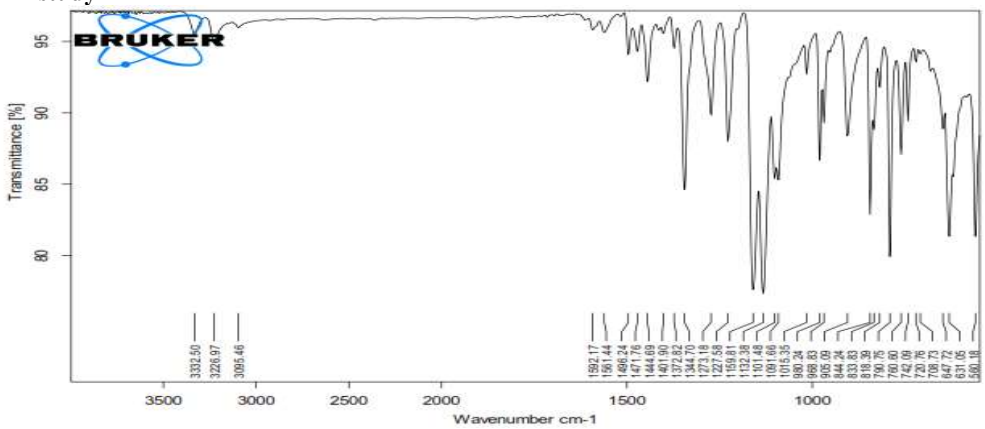

Fig 3: Ftir Graph Of Pure Drug

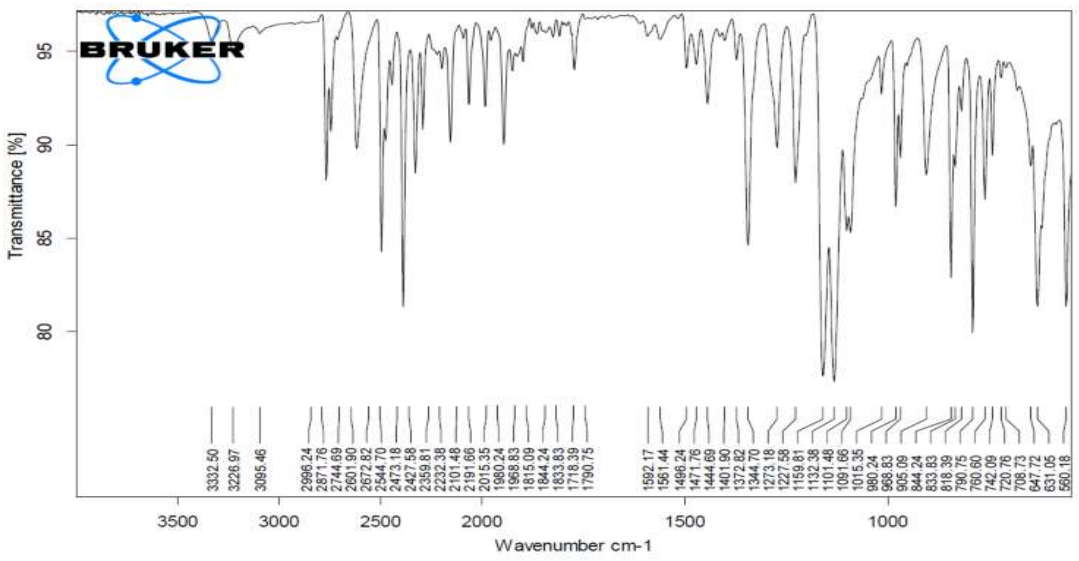

Fig 4: Ftir Graph Of Optimized Formulation

From the FTIR data is was evident that the drug and excipient does not have any interactions. Hence they were compatible.

EVALUATION PARAMETERS

Pre-compression parameters

Table 2: Pre-compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.18	0.41	0.49	16.32	1.19
F2	26.57	0.45	0.51	12.00	1.13
F3	25.22	0.47	0.54	12.96	1.14
F4	26.61	0.51	0.59	13.55	1.15
F5	27.41	0.49	0.57	14.03	1.16
F6	25.33	0.55	0.61	16.12	1.10
F7	26.25	0.43	0.51	15.68	1.18
F8	27.46	0.55	0.63	12.69	1.14
F9	26.23	0.57	0.66	13.63	1.15

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 25 to 30; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.41to 0.57 (gm/cm^3) showing that the powder has goof flow properties. The tapped density of all the formulations was found to be in the range of 0.49 to 0.66 showing he powder has good flow properties. The compressibility index of all the formulations was found to ranging from 12 to 16.32 which showed that the powder has good flow properties. All the formulations were showed the Hausner ratio ranging from 0 to 1.25 indicating the powder has good flow properties.

Post Compression Parameters For Tablets

Table 3: Post Compression Parameters Of Tablets

Formulation codes	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	200.23	3.8	0.52	4.5	98.15
F2	201.53	3.5	0.55	4.2	99.50
F3	199.25	3.6	0.48	4.4	99.41

F4	198.25	3.7	0.42	4.3	97.2
F5	202.5	3.7	0.57	4.2	99.3
F6	203.26	3.7	0.45	4.4	98.2
F7	199.5	3.8	0.56	4.3	98.36
F8	202.26	3.5	0.53	4.6	99.57
F9	201.36	3.7	0.54	4.5	98.8

Weight variation and thickness: all the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table .The average tablet weight of all the formulations was found to be between 198.25 to 203.26. The maximum allowed percentage weight variation for tablets weighing >200 mg is 5% and no formulations are not exceeding this limit . Thus all the formulations were found to comply with the standards given in I.P and thickness of all the formulations was also complying with the standards that were found to be between 4.2 to 4.6.

Hardness and friability: all the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table. The average hardness for all the formulations was found to be between (3.5to 3.8) kg/cm^2 which was found to be acceptable. Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table .The average percentage friability for all the formulations was between 0.42 and 0.57, which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in the methodology section and the results were shown in table. The drug content values for all the formulations were found to in range of (97.2 to 99.57). According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

***In vitro* drug release studies**

The formulations prepared with different polymers by direct compression method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1 N HCL for 2 hr and 6.8 pH phosphate buffer for remaining hours as a dissolution medium

Table 4: Dissolution Data of Indomethacin Tablets Prepared With Methyl Cellulose in Different Ratios

TIME	CUMULATIVE PERCENT DRUG RELEASED		
(hr)	F1	F2	F3
0	0	0	0
1	11.6	8.7	6.6
2	21.5	17.1	13.4
4	33.09	27.9	22.5
6	46.6	39.6	30.2
8	67.4	51.7	47.3
10	73.6	64.9	58.8
12	86.6	77.3	65.6
16	91.9	86.6	72.4
20	98.9	94.8	87.6
24	-	96.84	95.18

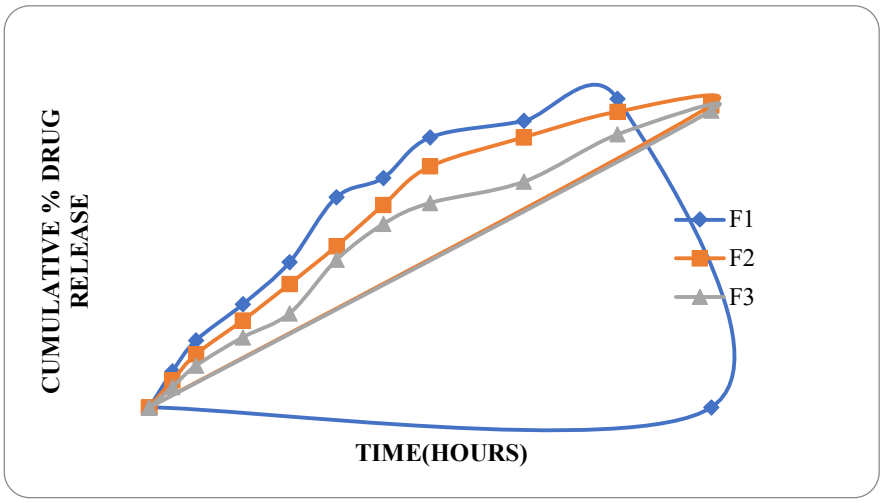

Fig 5:Dissolution study of Indomethacin Sustained Release tablets (F1 to F3)

Table 5: Dissolution Data of IndomethacinTablets Prepared with HPMC K4 M in Different Concentrations

TIME (hr)	CUMULATIVE PERCENTAGE DRUG RELEASED		
	F4	F5	F6
0	0	0	0
1	9.1	8.6	7.8
2	17.6	13.9	10.8
4	35.4	28.3	22.6
6	50.6	42.2	37.7
8	65.9	55.3	49.8
10	71.8	69.87	63.7
12	80.4	82.54	75.6
16	97.88	87.32	83.44
20	-	90.15	90.56
24	-	92.87	96.73

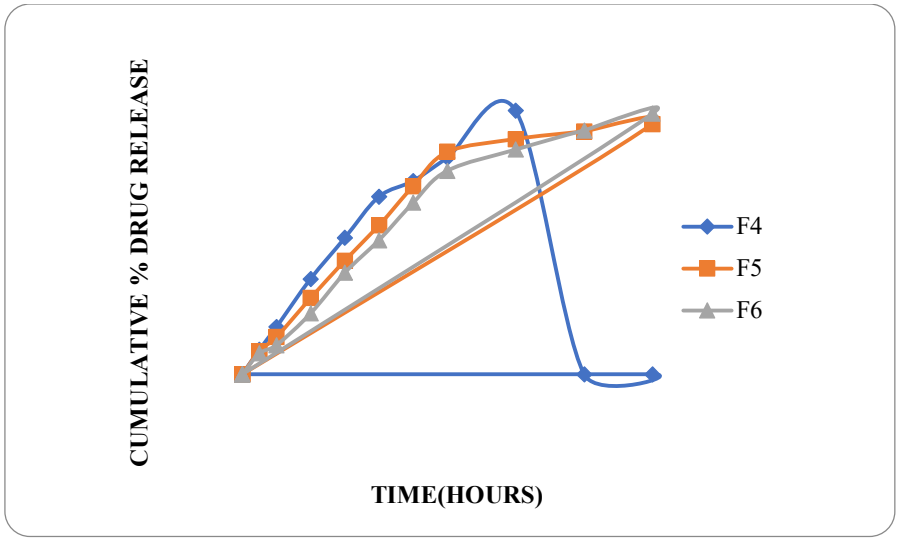

Fig 6: Dissolution study of Indomethacin tablets (F4 to F6)

Table 6: Dissolution Data of Indomethacin by using Hydroxy Ethyl Cellulose

TIME (hr)	CUMULATIVE PERCENTAGE DRUG RELEASED		
	F7	F8	F9
0	0	0	0
1	16.5	12.6	10.6
2	27.3	18.7	19.2
4	39.2	27.9	27.3
6	45.7	36.4	35.8
8	56.5	49.8	42.5
10	64.9	55.7	57.3
12	73.6	69.8	72.9
16	89.5	84.17	84.7
20	95.57	90.36	96.5
24	-	99.27	-

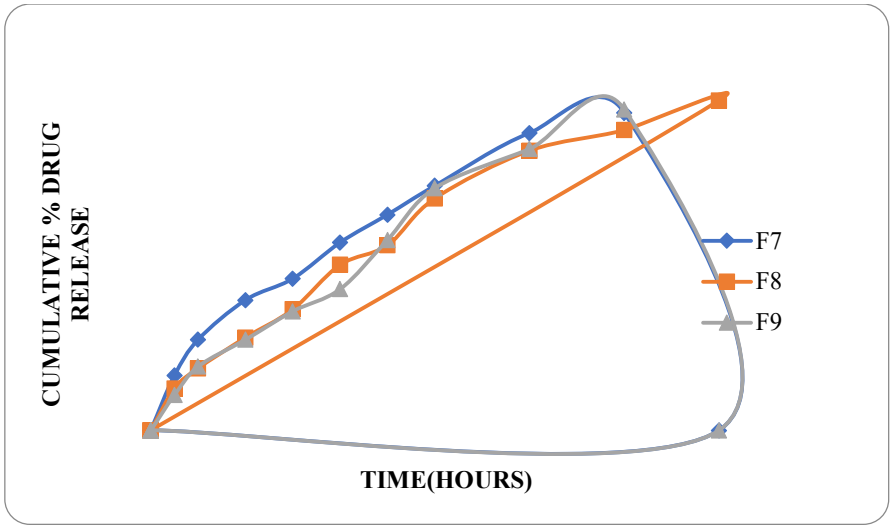

Fig 7: Dissolution study of Indomethacin tablets (F7-F9)

Among all the formulations F8 formulation containing (Drug : HEC) 1:1 ratio showed maximum % drug release i.e. 99.27% at 24 hr .

Hence based on dissolution data of 9 formulations, F8 formulation showed better release up to 24 hours. So F8 formulation is optimized formulation,

Application Of Release Rate Kinetics To Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Indomethacin release from sustained tablets. The data was fitted into various kinetic models such as zero, first order kinetics ,Higuchi and Korsmeyer peppas mechanisms and the results were shown in the below table.

Table 7: Release Kinetics data for optimized formulation(F8)

CUMULATIVE (%) RELEASE	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIV	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
12.6	1	1.000	1.100	0.000	1.942	12.600	0.0794	-0.900	87.4	4.642	4.438	0.204

18.7	2	1.414	1.272	0.301	1.910	9.350	0.0535	-0.728	81.3	4.642	4.332	0.310
27.9	4	2.000	1.446	0.602	1.858	6.975	0.0358	-0.554	72.1	4.642	4.162	0.479
36.4	6	2.449	1.561	0.778	1.803	6.067	0.0275	-0.439	63.6	4.642	3.992	0.650
49.8	8	2.828	1.697	0.903	1.701	6.225	0.0201	-0.303	50.2	4.642	3.689	0.953
55.7	10	3.162	1.746	1.000	1.646	5.570	0.0180	-0.254	44.3	4.642	3.538	1.103
69.8	12	3.464	1.844	1.079	1.480	5.817	0.0143	-0.156	30.2	4.642	3.114	1.527
84.17	16	4.000	1.925	1.204	1.199	5.261	0.0119	-0.075	15.83	4.642	2.511	2.131
90.36	20	4.472	1.956	1.301	0.984	4.518	0.0111	-0.044	9.64	4.642	2.128	2.513
99.27	24	4.899	1.997	1.380	-0.137	4.136	0.0101	-0.003	0.73	4.642	0.900	3.741

SUMMARY

In the present work the Sustained release tablets of Indomethacin were prepared by using various semi synthetic polymers like, Methyl cellulose, HPMC K4M, HEC in different ratios.

Initially analytical method development was done for the drug molecule. Absorption maxima was determined and the calibration curve was developed by using different concentrations.

The formulated sustained release tablets were evaluated for different parameters such as drug excipient compatability studies, weight variation, thickness, hardness, content uniformity and *In vitro* drug release. *In vitro* drug release studies performed in pH 1.2 and phosphate buffer pH 6.8 for 24 hours in standard dissolution apparatus. Among these semi synthetic polymers Hydroxyethylcellulose (HEC) shows the best release compare HPMC and Methyl cellulose. The formulation containing 1:1 ratio of (Indomethacin: HEC) showed maximum % drug release i.e 99.27 % at 24 hours. . The data was subjected to zero order, first order, Zero and First diffusion models.

The following conclusions could be drawn from the results of various experiments

- ✓ FTIR studies concluded that there was no interaction between drug and excipient.
- ✓ The physic-chemical properties of all the formulations prepared with different polymers like Methyl cellulose, HPMC K4M , HEC were shown to be within limits.
- ✓ Properties and from the results, it was concluded that the *in vitro* drug release of the optimized formulations is suitable for Sustained drug delivery system.

CONCLUSION

The present concludes that sustained drug delivery of Indomethacin can be good way to prolong duration of action of drug by reducing the dosing frequency of Indomethacin present study concludes that Sustained delivery system should be a suitable method for Indomethacin administration. The optimized formulation was found to be F8 formulation.

REFERENCES

1. Jain KK. Drug delivery systems. 1st edition. Switzerland: Human Press; 2008. P. 1-51.Reddy KR, Mutalik S, Reddy S.APPS Pharm. Sci. Tech .2003; 4:19. 121-125.
2. Chien YW. Novel drug delivery system. 2nd edition revised and expanded. New York: Informa health care; 2009. P. 1-50.
3. Jantzen GM, Robinson JR.Sustained and Controlled – Release Drug Delivery systems Modern Pharmaceutics, 4th ed; 2003; 121:501-502.
4. Salsa T, Veiga F. Drug Develop. Ind pharm. 1997;23:931.
5. Gwen MJ, Joseph RR, In Banker GS and Rhodes CT, Ed . Modern pharmaceutics, 3rd Ed Marcel Dekker Inc. New York . 1996; 72:575.
6. Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, in Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, 3rd Ed, Revised and expanded, Drugs and the Pharmaceutical Sciences ., Marcell Dekker, Inc. New York. 1995; 72:575-609.
7. Lee BJ, Ryu SG, Cui JH, Drug Dev. 1999; 25:493-501.
8. Vidyahara S, Rao PR , Prasad JA . Indian J Pharm Sci. 2004;66:188-192.
9. Bonger RH. Bioavailability and bioequivalence of extended-release oral dosage forms . US Pharmacist. 1997;22-3-12.
10. Rogers JD, Kwan KC. Pharmacokinetic requirements for controlled –release dosage forms. In: John Urquhart, ed. Controlled–release pharmaceuticals. Academy of Pharmaceutical Sciences. American Pharmaceutical Association. 1979:95-119.
11. Madan PL. Sustained-release drug delivery systems, part ii: Preformulation considerations. Pharm Manu fact. 1985;2:41-45.

12. Wani MS , Controlled Release System –A Review, 2008;61:56-62.
13. Banker GS , Anderson NR. The Theory and Practice of Industrial Pharmacy : Tablet Lachman (3rd ed) Varghese Publishing House , Bombay. 1990; 3: 293-303.
14. Manish R, Jayesh P, Siahboomi AR. Hydrophilic Matrices for Oral Extended Release : Influence of Fillers on Drug Release from HPMC Matrices . Pharma Times. 2010;4(2): 67-73.
15. Lee VHL, Controlled Drug Delivery Fundamentals and Applications : Influence of drug properties on design , Marcel Dekker, INC, and New York . 1987;2:16-29.