Formulation and In Vitro Evaluation of Isosorbide Mononitrate Sustained Release Tablets

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ABSTRACT:
The objective of the present study was to formulate sustained-release matrix tablets of Isosorbide Mononitrate, for treatment of Angina (Chest pain). The matrix tablets were prepared by direct compression method using various synthetic polymers in various concentrations. The powder showed satisfactory flow properties and compressibility. All the formulations showed acceptable pharmacopoeia standards. The result of formulation F5. Model fitting analysis for formulation F5 fitted in the zero-order model and Higuchi model. Successful formulation was found stable after evaluation for physicochemical parameters when kept for 90 days at room temperature, 40^0c and 2-8 ^{0} c. It concluded that sustained release matrix tablets of Isosorbide Mononitrate containing Ethyl cellulose provide a better option for the Sustained release of the drug.
Key words: Isosorbide Mononitrate, polymers, FTIR Studies, Direct compression technique, Sustained release matrix tablets, In vitro drug release studies.

I. INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes[1]. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are 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'[2]. Matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and palletisation 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.[3] Angina pectoris, a cardiovascular ailment, is identified by chest pain or discomfort brought on by an alteration in the amount of blood flowing to the heart. One of the drugs used for the treatment of this condition is Isosorbide dinitrate (ISDN), which belongs to the class of nitrate drugs. In order to increase blood flow to the heart and lessen the strain on the heart, ISDN works through dilation of blood vessels.[4]

II. EXPERIMENTAL WORK

MATERIALS

Isosorbide Mononitrate procured from Synpharma Research Labs, HYD. Eudragit RS100and Ethyl cellulosewas obtained from Synpharma Research Labs, Hyderabad. Other chemicalsand the reagents used were of analytical grade.

METHODOLOGY

Fourier Transform Infrared Spectroscopy (FTIR)[5]

FTIR spectroscopy Isosorbide Mononitrate discs were created by compressing the Isosorbide mononitrate with KBr and the spectra was scanned in the range between 4000 to 400 cm-1. Perfect operational conditions were maintained. The absorption maxima which is denoted as max in spectrum obtained with the drug substance is compared with the intensity to those of reference spectrum.

Preparation of Isosorbide Mononitrate tablets:

Table-1: Formulation Table of Isosorbide Mononitrate sustained release tablets

S.NO.	INGREDIENTS	F1	F 2	F 3	F 4	F5	F 6	F 7	F 8
1	Isosorbide Mononitrate	10	10	10	10	10	10	10	10
2	Eudragit RS100	25	50	75	100	-	-	-	-
3	Ethyl cellulose	-	-	-	-	25	50	75	100
6	Microcrystalline Cellulose	160	135	110	85	160	135	110	85
7	Magnesium stearate	3	3	3	3	3	3	3	3

8	Talc	2	2	2	2	2	2	2	2
9	Total Wt.	200	200	200	200	200	200	200	200

Direct compression technique[6]

Sustained release matrix tablets of Isosorbide Mononitrate were prepared by direct compression. All the ingredients were passed through 40- mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200mg using 100mm round flat punches on 8- station rotary tablet machine (Rimek).

Evaluation parameters

Weight variation:

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviates from the average weight by more than the percentage. [7]

Thickness:

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.[8]

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined. [9]

Friability:

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.[10]

The percentage friability was measured using the formula,

$\% F = \{1-(Wo/W)\} \times 100$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity:

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Isosorbide Mononitrate. Dissolve the weighed quantity of powder into 100 ml of 0.1 N NaOH solution by stirring it for 15 min. 01 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at nm using reagent blank.[11]

Disintegration time:

The disintegration time of tablets was determined by using Disintegration test apparatus (scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.[12]

***In- Vitro* Release study:**

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 100 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time. Temperature maintained at 37±5.The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask and make the volume with distilled water. The diluted samples were assayed at 256 nm against reagent blank. [13]

Kinetic modelling of drug release [14]

All the 8 formulation of prepared matrix tablets of Isosorbide Mononitrate were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Peppas Exponential Equation)

Stability studies:[15]

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared Matrix tablets of Isosorbide Mononitrate were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 90 days.

III. RESULTS AND DISCUSSION

FT-IR Spectrum of Isosorbide Mononitrate

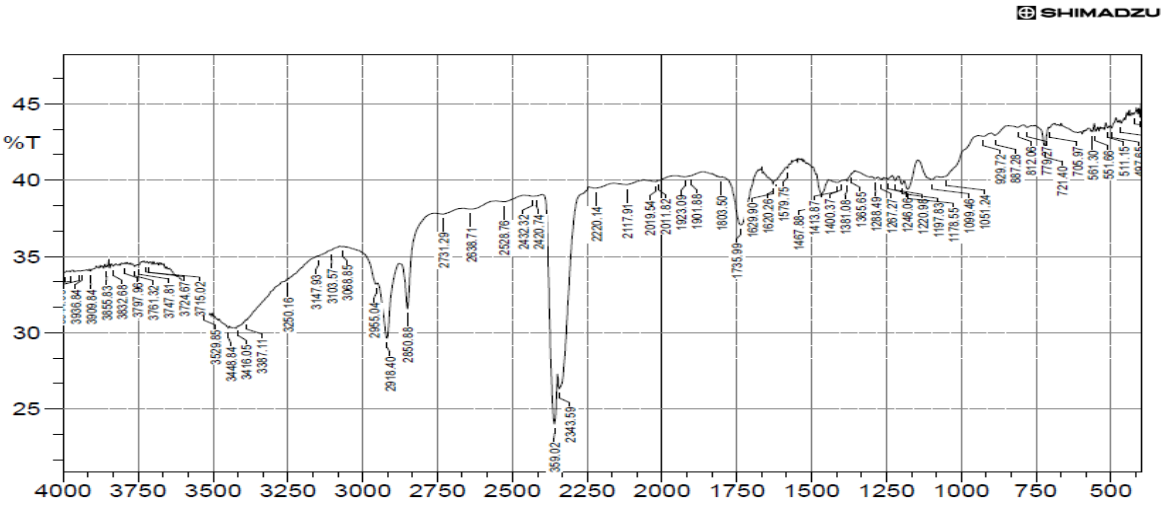

Fig-1: FTIR Spectra of Isosorbide Mononitrate

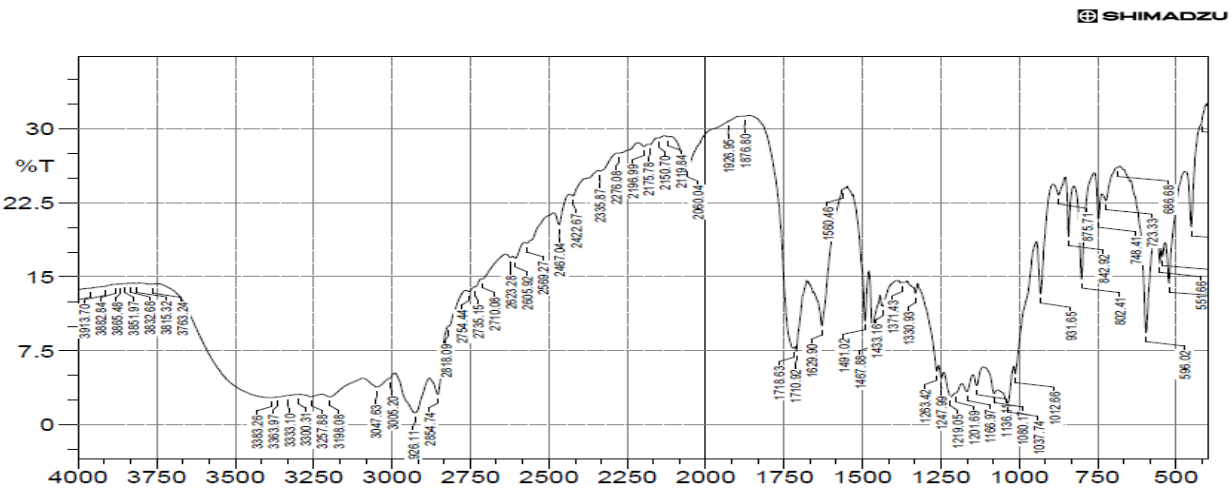

Fig-2:FT-IR graph for optimized formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Evaluation parameters

Weight variation:

All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 2.2 mm to 2.7 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 3.1 to 3.9 kg/cm^2. This ensures good handling characteristics of all batches.

Friability:

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F8 was found to be between 82.35 % to 89.85% of Isosorbide Mononitrate , it complies with official specifications.

Disintegration Time:

In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods.

Table-2: Evaluation parameters of Isosorbide Mononitrate SR tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time (min)
F1	200	2.3	3.2	0.28	86.52	13
F2	199	2.7	3.4	0.26	88.20	15
F3	200	2.6	3.7	0.29	84.13	12
F4	201	2.2	3.5	0.31	87.29	14
F5	200	2.5	3.8	0.34	82.35	16
F6	199	2.8	3.1	0.27	85.55	12
F7	200	2.6	3.9	0.32	89.85	9
F8	200	2.7	3.5	0.35	87.69	10

Dissolution studies

All the 8 formulation of Isosorbide Mononitrate tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-3: Drug release studies of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	17.53	17.40	18.10	17.96	19.13	18.64	19.30	18.50
2	26.89	25.98	27.50	29.15	29.99	28.16	26.59	27.53
3	37.52	37.80	39.11	38.13	39.67	37.50	36.48	35.46
4	53.60	54.51	55.55	55.16	57.81	57.46	52.21	53.11
5	65.10	66.71	65.93	65.22	68.91	69.50	64.52	65.82
6	72.89	72.98	72.86	73.69	79.76	76.50	73.65	74.86
7	82.43	83.59	83.64	81.26	86.70	86.49	85.41	82.91
8	94.10	95.15	95.10	96.63	98.36	96.72	95.68	94.67

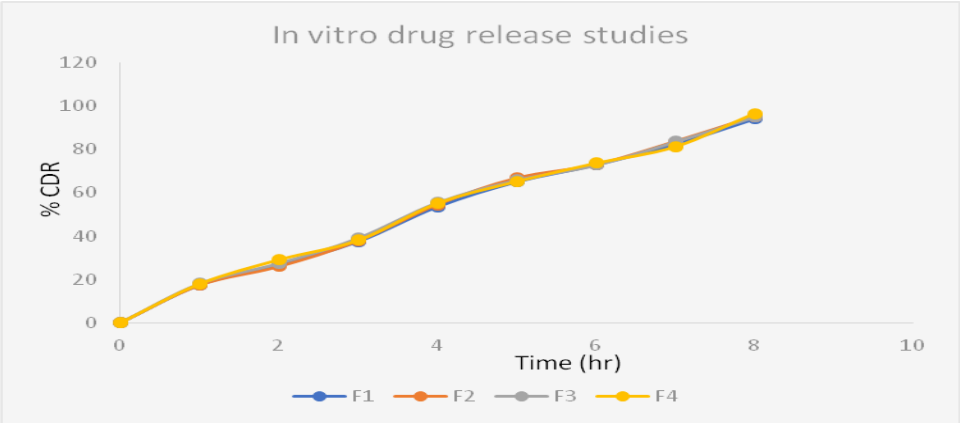

Fig-3: Dissolution Profile of F1 to F4 formulations

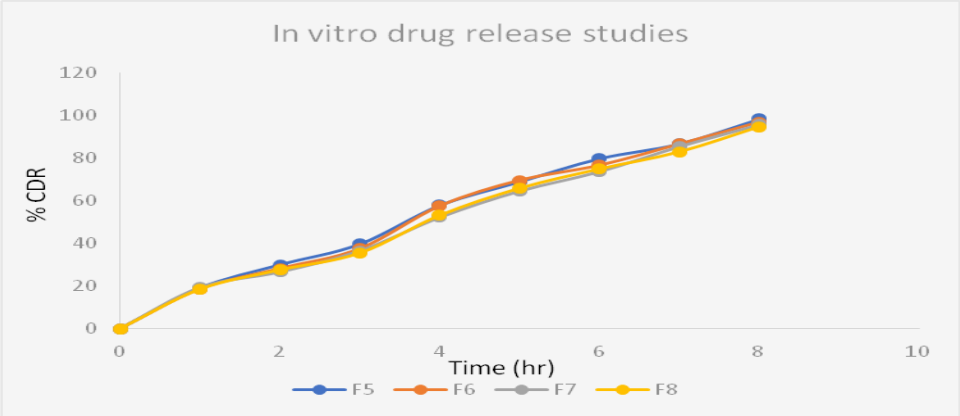

Fig-4: Dissolution Profile of F5 to F8 formulations

Cumulative Drug release of F5 formulation shows 98.36 % within 8 hr better drug release when compared with other formulations.

Kinetic modelling of drug release

All the 8 formulation of prepared matrix tablets of Isosorbide Mononitrate were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
4. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
5. Log of cumulative % release Vs log time (Peppas Exponential Equation)

Zero order kinetics

Fig-5: Zero order kinetics of optimized formulation

First order kinetics

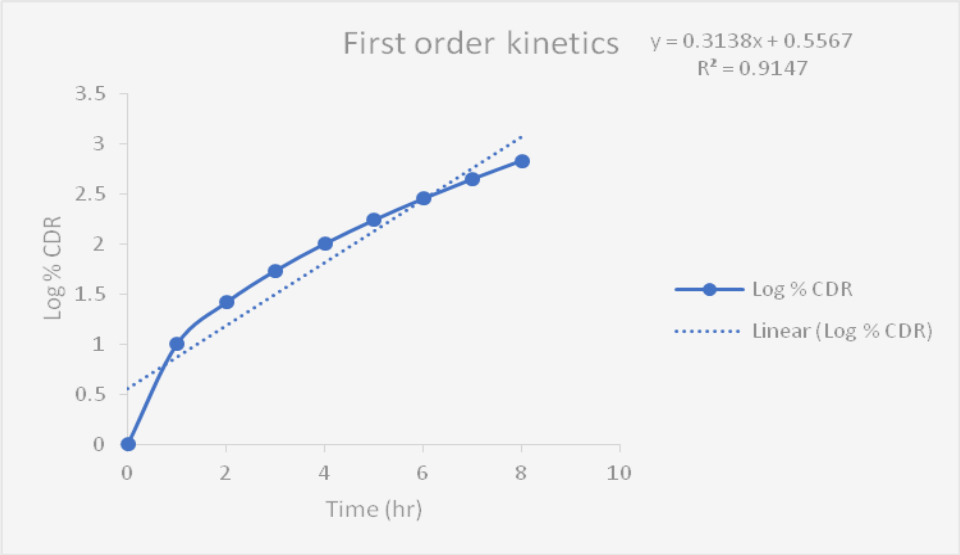

Fig-6: First order kinetics of optimized formulation

Higuchi model

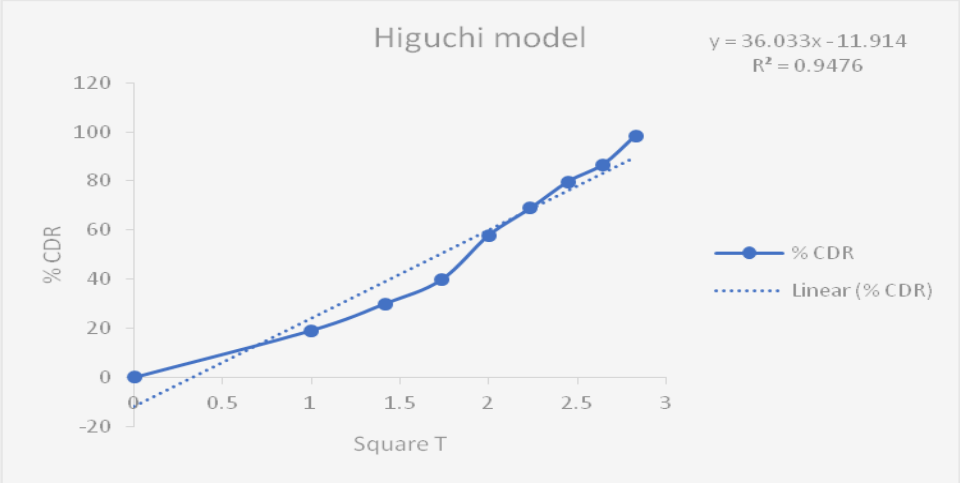

Fig-7: Higuchi model of optimized formulation

Korsmeyer peppas

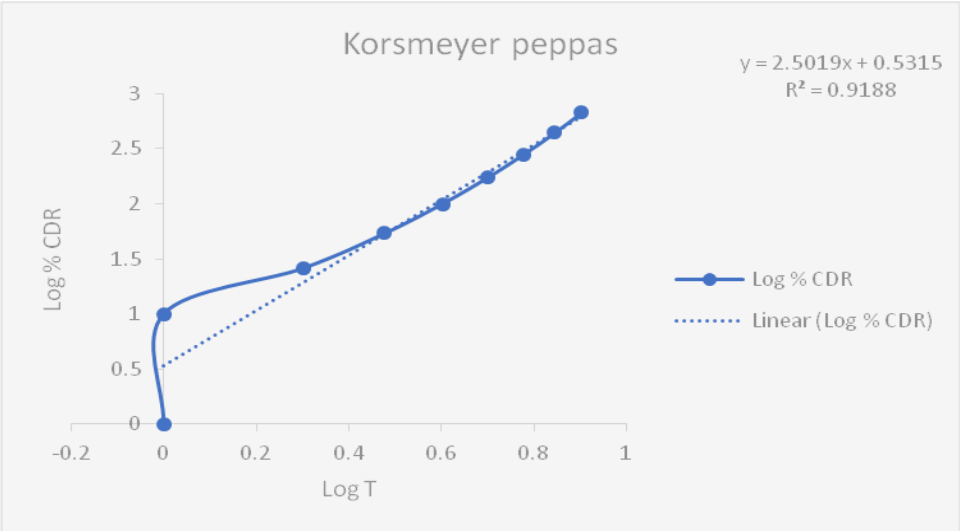

Fig-8: Korsmeyer peppas of optimized formulation

Regression values are higher with Zero order release kinetics. Therefore, all the Isosorbide Mononitrate Tablets follows

Zero order release kinetics.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-5 after 90 days. Parameters quantified at various time intervals were shown.

Table-4: Stability studies of all formulations

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-5	**25^0C/60%RH**	98.36	97.52	96.37	95.22	**Not less than**
F-5	**30^0C/75% RH**	98.36	97.16	96.35	95.16	**Not less than**
F-5	**40^0C/75% RH**	98.36	97.1	96.2	95.1	**Not less than**

CONCLUSION

The results of the present study indicate that sustained release tablets of Isosorbide Mononitrate withsustained drug release can be successfully prepared by direct compression method using Eudragit RS 100 and Ethyl cellulose.The formulation F5 containing Ethyl cellulose was found to be promising, which shows an in vitro drug release of 98.36 % in 8 h along with satisfactory results.From the above experimental results, it can be concluded that sustained-release tablets of Isosorbide Mononitrate can be prepared by using different proportions & combination of Excipients and we selected F5 as the best formulation based on dissolution profile and physical characteristics. Formulation (F5) showed total drug release in 8 hr and showed fair flow properties when compared to other formulations. The formulations F5, followed Zero order kinetics.

REFERENCES

1. Gupta PK and Robinson JR. Oral controlled release delivery. Treatise on controlled drug delivery. 1992;93(2):545-555. 2.
2. Jantzen GM and Robinson JR. Sustained and Controlled- Release Drug Delivery systems. Modern Pharmaceutics. 1995; 121(4): 501-502.
3. Altaf AS, Friend DR, MASRx and COSRx Sustained-Release Technology in Rathbone MJ, Hadgraft J, and Robert MS. Modified Release Drug Delivery Technology, Marcel Dekker Inc., New York, 2003; 126: 996.
4. Gwen MJ and Joseph RR, In Banker GS and Rhodes CT, Eds. Modern Pharmaceutics, Marcel Dekker Inc. New York, 1996; 72(3): 575.
5. Salsa T, Veiga F and Pina ME. Oral controlled release dosage form. I. cellulose ether polymers in hydrophilic matrices. Drug Develop. Ind. Pharm. 1997; 23: 929-938.
6. Wani MS et al. Controlled Release system-A Review. Pharmaceutical Reviews. 2008; 6(1): 41-46.
7. Altaf AS, Friend DR, MASRx and COSRx Sustained-Release Technology in Rathbone MJ, Hadgraft J, Robert MS, Modified Release Drug Delivery Technology, Marcell Dekker Inc., New York, 2003. JPSBR: Volume 1, Issue 3: Nov Dec 2011 (143-151) Patel H. 151
8. John JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, Bhat G. A comparison of enalapril with hydralazine–isosorbide dinitrate in the treatment of chronic congestive heart failure. New England Journal of Medicine. 1991 Aug 1;325(5):303-10
9. Arpitha G, Formulation and evaluation of sustained release matrix tablets of lornoxicam using natural and synthetic polymers, european journal of pharmaceutical and medical research, ejpmr, 2021,8(11), 362-401.
10. Asim pasha, formulation and evaluation of sustained release matrix tablet of lornoxicam by direct compression method, Journal of Pharmaceutical and Scientific Innovation www.jpsionline.com (ISSN: 2277–4572)
11. Shilpi Mishra, Formulation and Evaluation of Nifedipine Sustained Release Matrix Tablet Using Different Grade of Hpmc, International Journal of Pharmaceutical Research and Applications Volume 7, Issue 2 Mar-Apr 2022, pp: 1728-1736.
12. V. Rama rao, formulation and in-vitro evaluation of metformin sustained release matrix tablets, international journal of pharmaceutical sciences and research, 5486-5493.
13. Lateef, Formulation and Evaluation of Sustained Release Ibuprofen Matrix Tablets Using Starch from Maize Genotypes as Polymer, Volume & Issue: Volume 67 (2021) - Issue 2 (June 2021)
14. Hsiu-O Ho, Ying-Ku Lin. Investigations on the drug releasing mechanism from an Asymmetric membranecoated capsule with an in situ formed delivery orifice. J. Control. Rel. 2003; 89: 57-69.
15. Toshiaki Nagakura, Ken Ishihara, Toshiyuki Furukawa, Kohji Masuda, Takao Tsuda. Auto-regulated Osmotic pump for insulin therapy by sensing glucose concentration without energy supply. Sensors and Actuators B. 1996; 34: 229-233.