IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
August 2023 Vol.:28, Issue:1

Formulation and *In-Vitro* Evaluation of Controlled Porosity Osmotic Pump Tablets of Montelukast Sodium

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
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ISSN 2349-7203
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Submitted: 25 July 2023
Accepted: 18 August 2023
Published: 30 August 2023

Keywords: controlled porosity osmotic tablet, semipermeable membrane, bioavailability, dissolution, pore forming material.

ABSTRACT

Objective: the present investigation was undertaken with the objective of formulating and evaluating controlled porosity osmotic tablets of montelukast sodium to enhance bioavailability and patient compliance for the treatment of asthma. **Methods:** nine different formulations of controlled porosity tablets of montelukast sodium were designed and manufactured by direct compression method using different concentrations of sodium chloride, mannitol, and lactose as osmogents. The cpop tablets were coated with cellulose acetate as a wall-forming material, polyethylene glycol 6000 as plasticizer, sodium lauryl sulphate as pore forming material in semipermeable membrane and ipa as a solvent. Dissolution and assay tests were performed using usp apparatus ii and ultraviolet (uv) spectrophotometry, respectively. The membrane morphology of the formulation was determined by scanning electron microscopy. Formulations with better results were further demonstrated for optimization studies. **Results:** the optimized formulation f8c2 had no significant effect on the ph and agitation intensity and has shown a controlled delivery of 94.99±0.28 for 8 hours. Sem images revealed that no pores were found before dissolution and after dissolution had showed the porous nature of the membrane. Short-term stability study at 40±2ºc /75±5% rh for the three months on the f8c2 formulation indicated that there was no significant change weight variation, % friability, drug content and in vitro drug release. **Conclusion:** the outcomes show that the formulation F8C2 is suitable as controlled porosity osmotic tablets of montelukast sodium to asthmatic patients in a convenient manner.

INTRODUCTION

Oral drug administration is the most preferred and common route for existing and new drug delivery The simplicity of its administration may be the cause [1]. Although, sometimes it also entails certain major disadvantages such as first-pass metabolism, gastrointestinal enzymatic degradation, and poor bioavailability. The sustained/controlled medication delivery method was developed to address the previous disadvantages of the traditional dose form.

Conventional drug delivery systems have small control over their drug release and almost no control over the successful concentration at the target site. This kind of dosing pattern may result in continuously varying, random plasma concentrations [2]. Drugs can be delivered in a controlled prototype over a long period of time by the controlled or altered release drug delivery systems. They contain dosage forms for oral and transdermal organization as well as injectable and implantable systems. For most of drugs, oral route remains as the most satisfactory route of administration.

The osmotic drug delivery system is a significant advancement for oral NDDS. A better pattern of delivery is to deliver the drug from a sustain release system which releases at slow rate throughout the delivery period. Several advancements have been made in the development of new drug delivery. They are Capable of controlling rate of drug delivery, Sustaining the duration of therapeutic activity and targeting the delivery of drugs to tissues [18]. Many innovative methods have been developed for controlling drug release. One among them is Controlled Porosity Osmotic Pump (CPOP) [3]. It is best approach for developing controlled-release dosage form. It is most reliable and employed as an oral drug delivery systems. The CPOP delivers the drug in sustained manner.

In the osmotic Controlled drug delivery system, the osmotic pressure is employed as the driving force to release the therapeutic agent in a controlled way. For the same purpose different techniques are used but this technique is most interesting and widely acceptable. Osmotic drug delivery system consists of tablet core that is coated with semipermeable membrane that has an orifice drilled. Therapeutic agents can be effectively delivered in controlled pattern over a long period of time.

In this present research work controlled porosity osmotic tablet is formulated using direct compression method. The montelukast sodium is a leukotriene receptor antagonist used for the treatment of asthma, and chronic asthma attacks and to relieve symptoms of seasonal

allergies [17]. Asthma is a chronic inflammatory disorder of the airways. It is characterized by Airway inflammatory cells, including eosinophils, macrophages, mast cells, epithelial cells and activated lymphocytes that release various cytokines, adhesion molecules and other mediators and Inflammation resulting in an acute, sub-acute or chronic process that alters airway tone, modulates vascular permeability, activates neurons, increases secretion of mucus and alters airway structure reversibly or permanently[16]. Montelukast is in a class of medications called leukotriene receptor antagonists (LTRAs). It works by blocking the action of substances in the body that are caused by the symptoms of asthma and allergic rhinitis. Montelukast sodium usual dosage regimen is 10mg taken single dose in a day having biological half-life of 2.2 to 5.5 hours and has decreasing bioavailability of 64%.

If patient is taking it more frequently of montelukast sodium it shows some common side-effects that includes upper respiratory infection, fever, headache, sore throat, cough, stomach pain, diarrhoea, earache or ear infection, flu, runny nose, and sinus infection. Therefore, the aim of the present work was to develop a new controlled porosity osmotic tablet of montelukast sodium. The osmotic tablet was prepared and evaluated by using different osmotic agents of Mannitol, sodium chloride, lactose and swellable polymers [4]. The objective of the research work is to enhance bioavailability, improve patient compliance and maintain Consistent blood plasma levels within the therapeutic window of the controlled porosity osmotic tablets of montelukast sodium.

MATERIALS AND METHODS

MATERIALS

Montelukast sodium API was procured as gift sample from Intermed Pharmaceuticals Pure, Chennai. Mannitol, sodium chloride, lactose, HPMC K4M, HPMC K100M and sodium lauryl sulphate were obtained from Intermed pharmaceuticals porur, Chennai.

METHODS

The pure drug and excipient compatibility was studied by FTIR spectrometry. The osmotic drug was formulated by direct compression method and undergone preformulation and post-formulation evaluation studies.

Formulation of controlled porosity osmotic tablets of montelukast sodium by direct compression method

Preparation of core tablets

Osmotic tablets of montelukast sodium was prepared by direct compression method by using as mannitol, lactose, sodium chloride as osmotic agents and HPMCK4M, HPMCK100M as swellable polymers. microcrystalline cellulose as diluents, magnesium stearate as lubricant, talc used as glidants. Before going to direct compression all the ingredients were screened through sieve no.60, except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 20 min[6]. After sufficient mixing lubricant was added and again mixed for an additional 2-4 min. Before compression, hardness was adjusted and compressed into 190 mg each tablets using tablet compression machine equipped with 10mm shallow concave punches on 8 station rotary tablet machine (the Cadmach compression machine) and the same hardness was used for the required number tablets. The various formulations designed are shown in Table 1.

Preparation of the coating solution

The CPOP tablets were coated with cellulose acetate as a wall-forming material, polyethylene glycol 6000 as plasticizer, sodium lauryl sulphate acts as pore-forming material in semipermeable membrane and IPA as a solvent. Three coating solutions of 3%, 6% and 9% were prepared for coating the tablets. The cellulose acetate was dissolved in small quantity of isopropyl alcohol. And then to this above mixture ethyl cellulose, Hpmc 5cps were added and stirred well until the mixture gets dissolved [7]. Then PEG was separately dissolved in small quantity of isopropyl alcohol and stirred well. Then this was added to the above mixture and to this tartrazine colouring agent was added and stirred for 30 mins in mechanical stirrer.

COATING CONDITIONS

Stainless steel pan with 200cm diameter

Rotation of the pan - 50 rpm

Nozzle diameter of a spray gun -1mm

Spray rate - 2ml / min

Drying temperature -60 °c

Table no.1: Different formulations for tablet

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Montelukast sodium	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Mannitol	90	70	-	-	-	-	70	90	-
Sodium chloride	-	-	-	-	40	60	40	60	60
Lactose	70	50	60	95	-	-	-	-	-
HPMC K4M	25	45	25	-	25	45	-	45	45
HPMC K100M	15	-	15	45	15	25	15	-	-
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	2	2	2	2	2	2	2	2	2
Microcrystalline cellulose	8	18	83	43	103	53	38	8	78
TOTAL	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**

Table no.2: Different formulations for coating solutions

Ingredients	**3 %**	**6%**	**9%**
Cellulose acetate	2	4	6
Ethylcellulose	-	2	1
HPMC 5 cps	1	-	2
PEG 6000	1	2	1
Sodium lauryl sulphate	2	4	8
Isopropyl alcohol	q.s	q.s	q.s
Tartrazine	0.5ml	0.5ml	0.5ml
TOTAL	**206mg**	**212mg**	**218mg**

EVALUATION OF TABLET PROPERTIES

a) Weight variation test:

20 tablets were selected randomly, each tablet was weighed in a single pan electronic balance and the average weight was calculated. The uniformity of the tablet was determined according to I.P. specifications [5].

b) Thickness:

The thickness of the tablet was measured using Vernier calliper and expressed in millimetres. It was determined by checking the thickness of ten tablets of each formulation. ±5% may be allowed depending on the size of the tablet [20].

c) Hardness test:

Tablets require a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping[14]. The hardness of the tablets was measured using tablet hardness tester. The hardness is measured in terms of kg/cm². 10 Tablets were chosen randomly and tested for hardness. The average hardness of 10 determinations was recorded [8].

d) Friability:

10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche Friabilator and rotated at the speed of 25 rpm for 100 revolutions [27]. The tablets were then removed from the Friabilator, dusted off the fines and again weighed and the weight was recorded. Percentage friability will be calculated by using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of the Tablets } (W_1) - \text{Final weight of the Tablets } (W_2)}{\text{Initial weight of the Tablets } (W_1)} \times 100$$

e) Swelling index:

The initial weight of the tablets (W_1) was noted and placed individually into Petri dish containing 10 ml of pH 6.8 buffer[26]. The weight of the tablets (W_2) was noted after every hour for 8 hours after wiping out the excess of water using filter paper. The swelling index will be calculated using the formula:

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100$$

f) *In-vitro* Dissolution study

The dissolution rate was studied using USP type II apparatus at 50 rpm (USP XXIII dissolution test apparatus) using 1000ml of pH 1.2 buffer for first 2 hours and 6.8 phosphate buffer for the rest of 6 hours[24]. Temperature of dissolution medium was maintained at 37±0.5ºC, aliquot of the dissolution medium was withdrawn at every 1 hour interval and filtered[11]. The absorbance of filtered solution was checked by UV spectrophotometric method at 240 nm and the concentration of drug was determined from standard calibration curve[13]. Dissolution rate was studied for all designed formulations and the results are shown in table with graphical representation.

Apparatus used : USP paddle type 2 dissolution test apparatus

Dissolution medium : 0.1N Hcl pH 1.2 and phosphate buffer pH 7.4

Dissolution medium volume : 900 ml

Temperature : 37± 0.5℃

Speed of paddle : 50 rpm

Sampling interval : 1 hour

Sample withdrawn : 5ml

Absorbance measure : 240 nm

g) Assay

Randomly tablets were weighted and crushed in a mortar then weighed powder contained equivalent to 10 mg of drug transferred in 100ml of 0.5% of SLS solution to give a concentration of 100 µg/ ml. Then 15ml of this solution and diluted up to 100ml with 0.5% of SLS solution to give a concentration of 15µg/ml. Absorbance was measured at 240nm using uv visible Spectrophotometer[9].

h) Scanning electron microscopy:

The surface morphology of tablet coating layer before and after dissolution was examined by scanning electron microscopy [10].

EVALUATION OF OPTIMIZED FORMULATION

Effect of agitational rates on drug release:

In order to study the effect of agitation intensity, release studies were performed for optimized formulations in dissolution apparatus at various rotational speeds of 50,100 and 150 rpm and the in vitro release studies of the tablets were conducted[21].

Effect of Osmogen concentration on drug release:

Release studies of the optimized formulation were conducted in release media of different osmotic pressure. To increase the osmotic pressure of the release media different osmogens were added. The release was studied at predetermined time intervals [25].

Effect of pH on drug release:

To study the effect of pH of release medium in the drug release of optimized formulation, the *in-vitro* release study was carried out in buffers of different pH of 0.1N Hcl, pH 6.8 of phosphate buffer and pH 7.4 of phosphate buffer in USP type II dissolution apparatus[22]. The release was studied at predetermined time intervals.

Effect of coat thickness:

To study the effect of coat thickness of the semipermeable membrane on drug release, core tablets of montelukast sodium were coated in different percentages (3%, 6% and 9%)[23]. The release profile of tablet was determined.

i) Stability studies:

The stability studies were carried out of the most satisfactory formulation as per ICH guidelines to assess the drug and formulation stability. The most satisfactory formulation was sealed in aluminium packaging and kept in humidity chamber maintained at 40 ± 2˚C, 75 ± 5% for three months[12]. At the end of the studies, samples were analysed for the post-compression parameters like physical properties, dissolution, and drug content.

Table no.3 stability storage conditions

S. No	Storage conditions	Test period (3 months)	
		Initial	Final
1.	40℃ ± 2℃ / 75 % ± 5 % RH	1st day	90th day

RESULTS

Raw material analysis

Montelukast sodium was analysed for various physical characteristics and was found to comply with IP.

Table no.4: Physical characters of montelukast sodium were found as per values obtained after analysis:

PARAMETER	SPECIFICATION AS PER IP	INFERENCE
Nature	hygroscopic, white to off-white powder	hygroscopic, white to off-white powder
colour	white to pale yellowish-white powder	white to pale yellowish-white powder
Odour	Odourless	Odourless

Solubility

It is extremely soluble in methanol and ethanol (99.5%) and easily soluble in water.

STANDARD CALIBRATION CURVE OF MONTELUKAST SODIUM:

Standard calibration for montelukast sodium was performed and results are mentioned in the table,

Table no.5: Standard calibration curve of montelukast sodium

S.NO.	CONCENTRATION (µg/ ml)	ABSORBANCE (nm)
1	5	0.036
2	10	0.067
3	15	0.093
4	20	0.113
5	25	0. 173

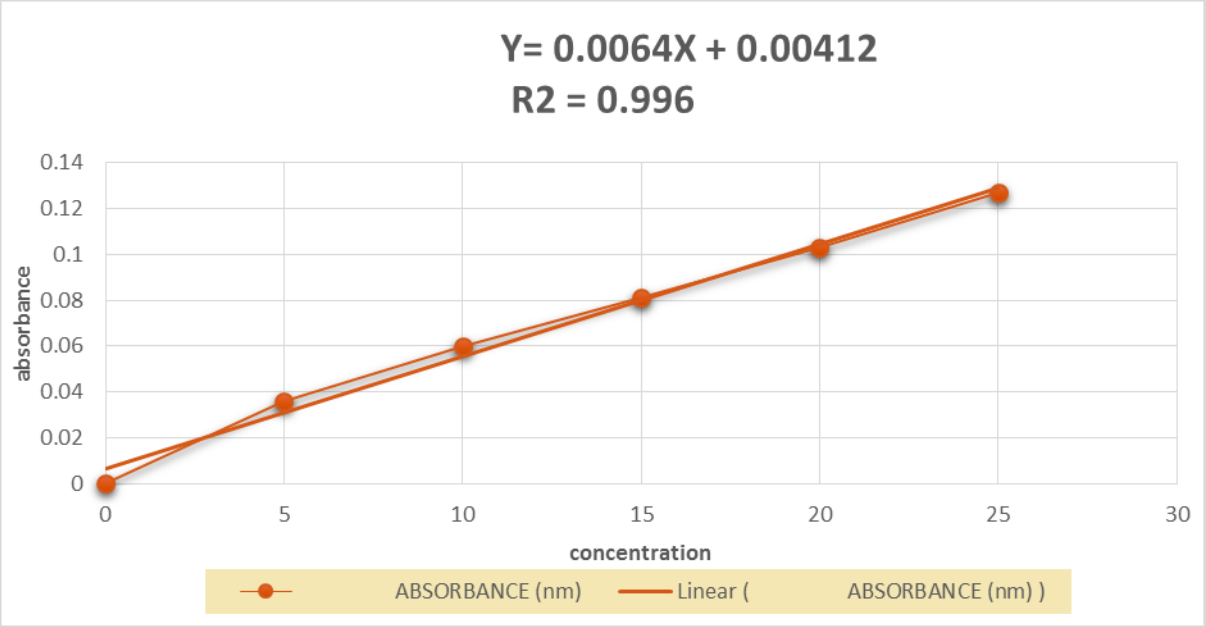


Fig.1: Standard Calibration Curve

COMPATIBILITY STUDIES:

Compatibility studies were performed using FT-IR spectrophotometry. The spectrum of pure drug and physical mixture of drugs and excipients were studied. The peak obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicated that the drug was compatible with formulation components. The spectra for all formulations are shown in the figure.

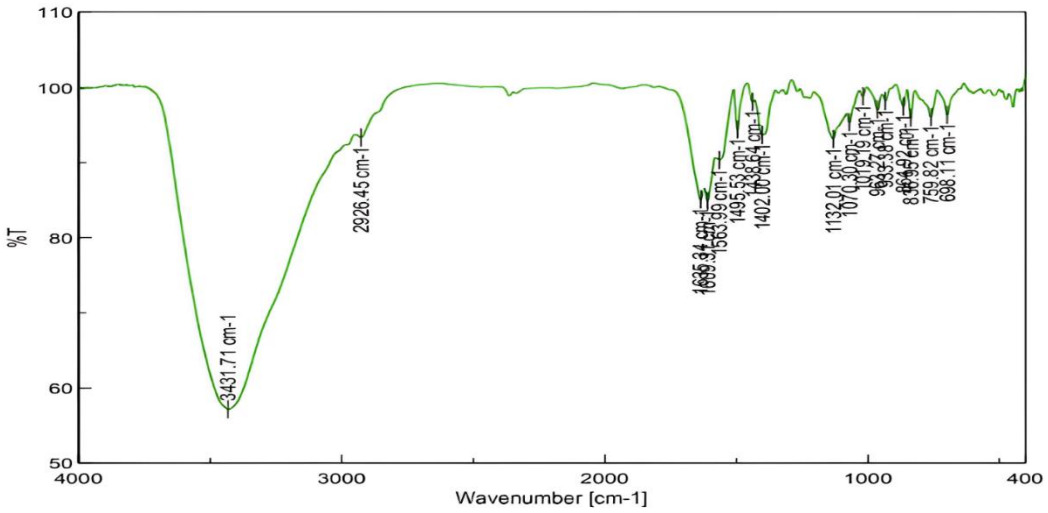


Fig.2: FT-IR of pure drug Montelukast Sodium

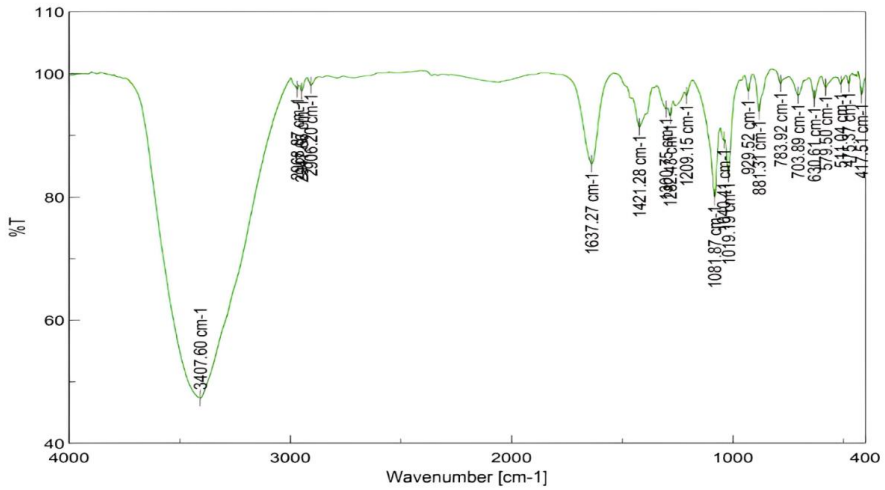


fig.3: FT-IR of mixture of Montelukast Sodium and Mannitol

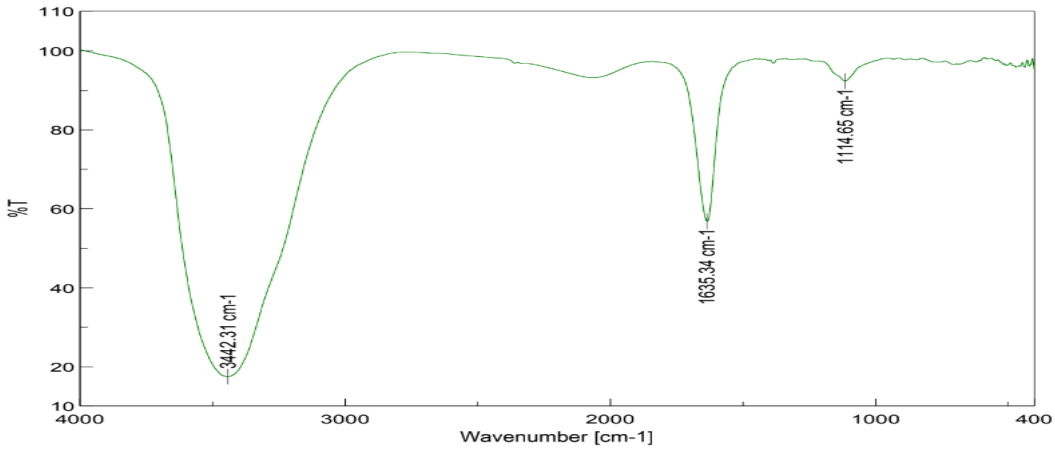


fig.4: FT-IR of mixture of montelukast sodium and sodium chloride

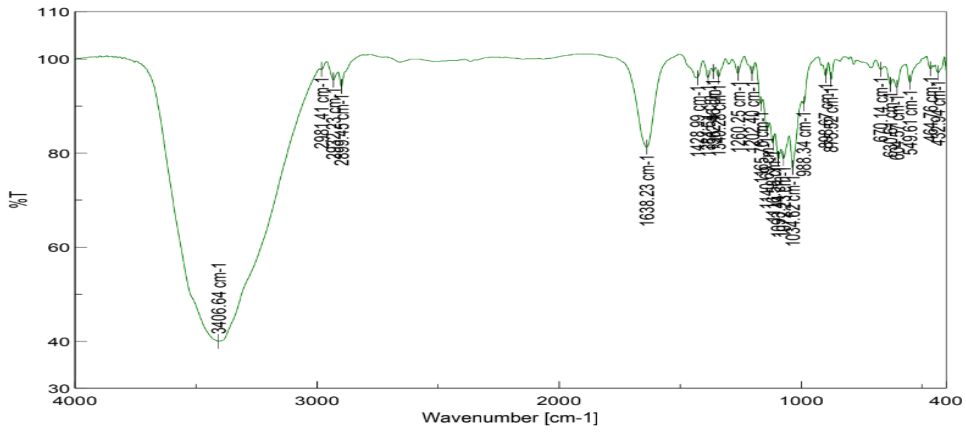


fig.5: FT-IR of mixture of montelukast sodium and lactose

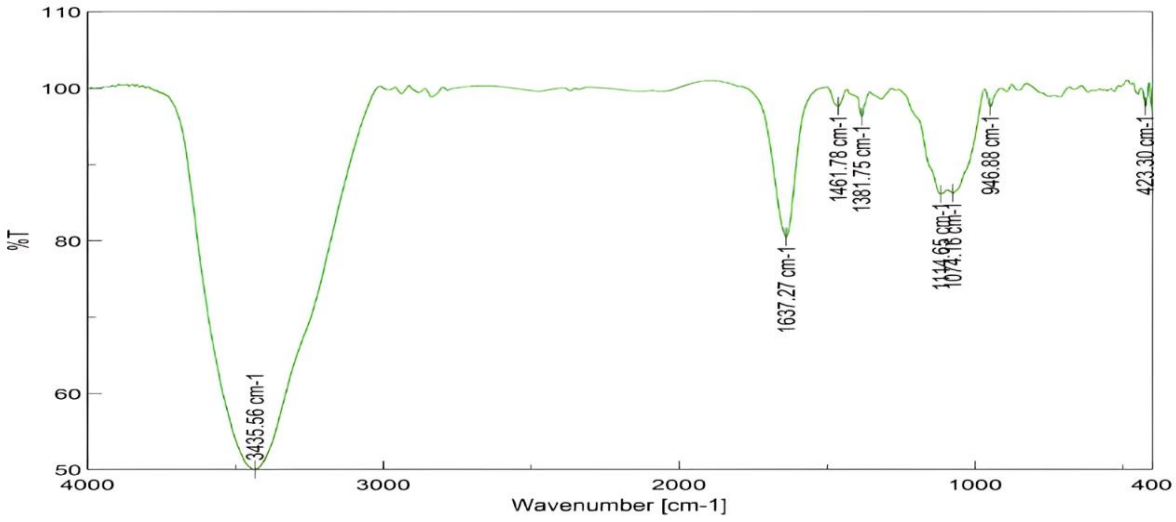


Fig.6: FT-IR of mixture of montelukast sodium and HPMC K4M

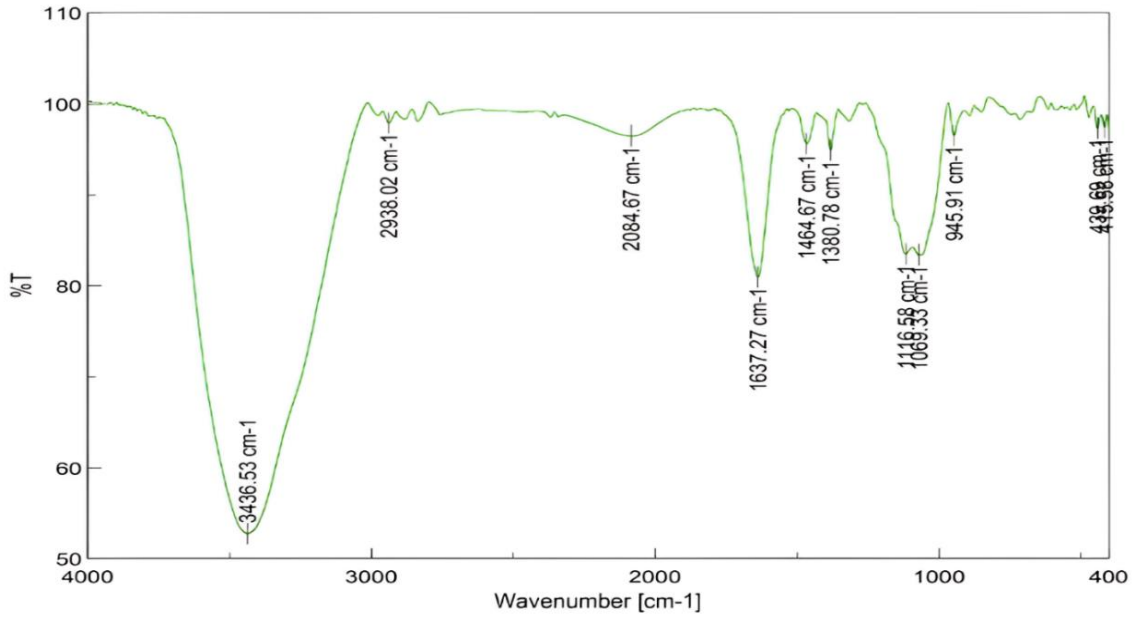


Fig.7: FT-IR of the mixture of montelukast sodium and HPMC K100M

Table no.6: FT-IR interpretation of montelukast sodium

Materials	Test wave number (cm^{-1})	Functional group assignment
Montelukast sodium	3431.71	C-OOH Stretching
	2926.45	C-H Stretching
	1609.31	C-O Bending
	1563.99	N-O Stretching
	1495.53	
	1402.00	
	1132.01	C-O Stretching
	1070.30	
	836.95	C=C Stretching
	759.82	

Table no.7: FT-IR interpretation of the physical mixture of montelukast sodium and Mannitol

Materials	Test wave number (cm^{-1})	Functional group assignment
Drug + Mannitol	3407.60	O-H Stretching
	2968.87	C-H Stretching
	2606.20	
	2947.87	
	1637.27	C=C Stretching
	1421.28	N-O Stretching
	1081.87	C-O Stretching
	1019.19	C-F Stretching
	1040.41	
	929.52	C=C Stretching
	630.61	C-Br Stretching

Table no.8: FT-IR interpretation of the physical mixture of montelukast sodium and sodium chloride

Materials	Test wave number (cm^{-1})	Functional group assignment
Drug +Sodium Chloride	3442.31	O-H Stretching
	1635.34	C=C Stretching
	1114.65	C-O Stretching

Table no.9: FT-IR interpretation of the physical mixture of montelukast sodium and Lactose

Materials	Test wave number (cm^{-1})	Functional group assignment
Drug +Lactose	3406.64	O-H Stretching
	2981.41	C-H_2Stretching
	2932.23	
	2899.5	
	1638.23	C=O Stretching
	1165.76	C-O Stretching
	1428.99	O-H Bending
	1340.28	
	1034.62	C-N Stretching
	988.34	C=C Stretching

Table no.10: FTIR interpretation of physical mixture of montelukast sodium and HPMC K4M

Materials	Test wave number (cm^{-1})	Functional group assignment
Drug + HPMC K4m	3435.56	O-H Stretching
	1637.27	C-H Stretching
	1461.78	N-O Stretching
	1381.75	C-H Bending
	1114.65	C-O Stretching
	1074.16	
	946.88	C=C Bending

Table no.11: FTIR interpretation of physical mixture of montelukast sodium and HPMC K100M

Materials	Test wave number (cm^{-1})	Functional group assignment
Drug + HPMC K100m	3436.53	O-H Stretching
	2938.02	N-H Stretching
	2084.67	N=C=S Stretching
	1637.27	C-H Bending
	1380.78	
	945.91	C=C Bending

PREFORMULATION STUDIES OF MONTELUKAST SODIUM OSMOTIC CORE TABLETS

Powder characterization: The blended powder of different were evaluated for angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The results of these evaluations are as follows.

a) Angle of repose(θ) :

The angle of repose for the blended was shown in Table No. 12. The angle of repose was found to be in the range of 22º.05±0.368´ to 25º.78±0.341. ´

b) Bulk density and tapped density:

Bulk density and tapped density are used for the measurements of compressibility index are shown in the Table No. 12. The bulk density and tapped density ranged from 0.451±0.10 to 0.489± 0.32 and 0.521±0.005 to 0.566±0.304.

c) Compressibility index (Carr's index):

The compressibility index is an important measure that can be obtained from the bulk and tapped density. The values are shown in the table no.12. Compressibility index is in the range from 10.076±1.0 to 14.763±7.2%.

d) Hausner's ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density. Hausner's ratio ranges from 1.13±0.02 to 1.202±0.40 as shown in table no.12.

Table no.12: Results of pre-formulation studies.

Formulation code	Angle of repose (Ɵ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's Ratio (%)	Carr's index (%)
F1	22.45±0.342	0.455±0.15	0.533±0.008	1.177±0.024	14.634%±5.4
F2	22.31±0.337	0.489±0.32	0.561±0.016	1.202±0.40	12.834%±6.6
F3	24.43±0.328	0.465±0.31	0.536±0.0212	1.152±0.34	13.246%±5.9
F4	22.05±0.368	0.479±0.12	0.562±0.019	1.195±0.29	14.763%±7.2
F5	22.34±0.379	0.473±0.24	0.566±0.265	1.196±0.36	10.076%±1.0
F6	24.29±0.348	0.476±0.18	0.539±0.008	1.132±0.02	11.688%±6.4
F7	23.89±0.375	0.483±0.22	0.549±0.023	1.136±0.08	12.021%±2.0
F8	25.78±0.341	0.462±0.19	0.532±0.017	1.151±0.25	13.157%±4.6
F9	24.98±0.374	0.451±0.10	0.521±0.005	1.155±0.39	13.435%±7.2

***Mean± SD (n = 3)**

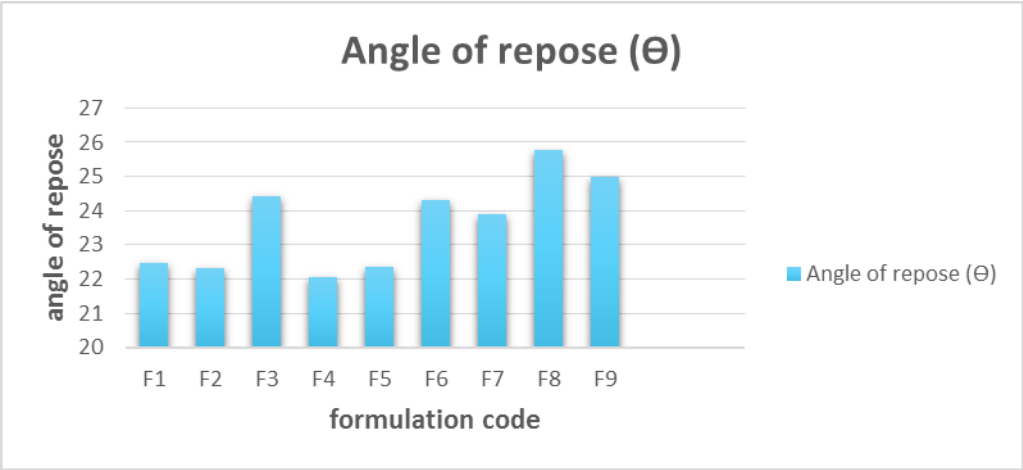


Fig.8: Figure of angle of repose results

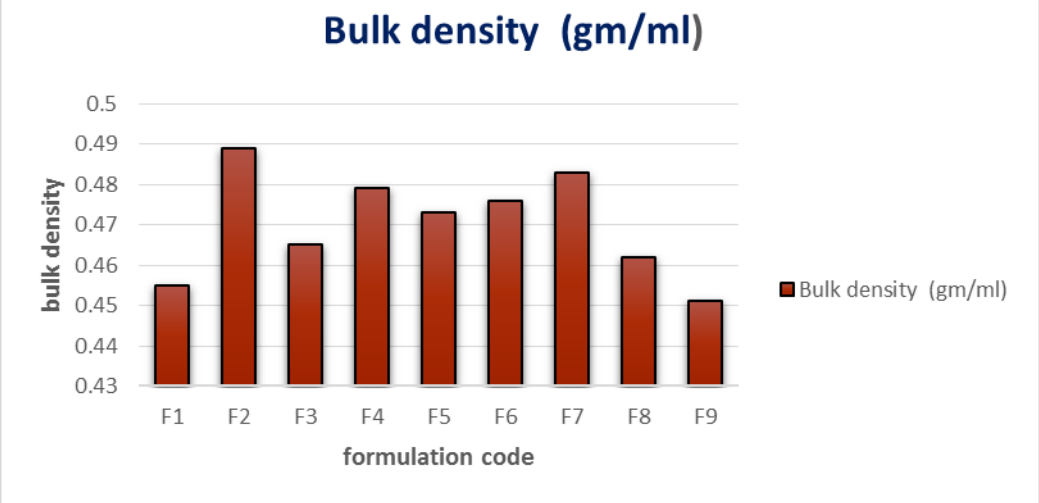


Fig.9: Figure of bulk density results

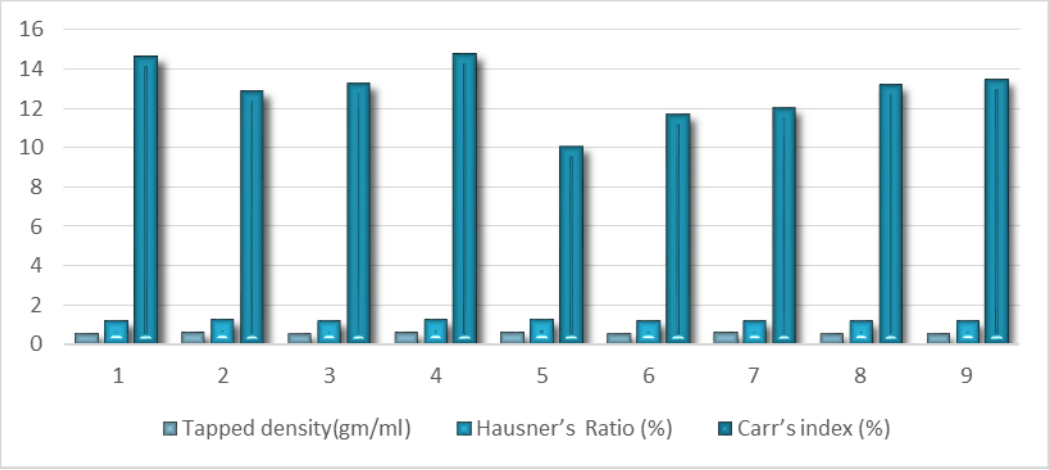


Fig .10: Figure of tapped density, Hausner's ratio and carr's index results

9.5. EVALUATION TEST OF MONTELUKAST SODIUM OSMOTIC CORE TABLET

Montelukast sodium osmotic core tablets were evaluated for various physical parameters namely thickness, hardness, friability, weight variation and uniformity of drug content.

Table no.13: Hardness and thickness results

Formulation code	Hardness of the tablet (Kg/cm^2)	Thickness of the tablet (mm)
F1	4.4±0.16	0.343±0.03
F2	4.3±0.62	0.413±0.02
F3	4.1±0.25	0.534±0.04
F4	3.9±0.57	0.319±0.03
F5	3.8±0.28	0.426±0.02
F6	4.0 ±0.47	0.491±0.05
F7	4.2±0.78	0.447±0.03
F8	3.9±0.42	0.482±0.02
F9	3.8±0.38	0.413±0.04

* **Mean SD (n = 3)**

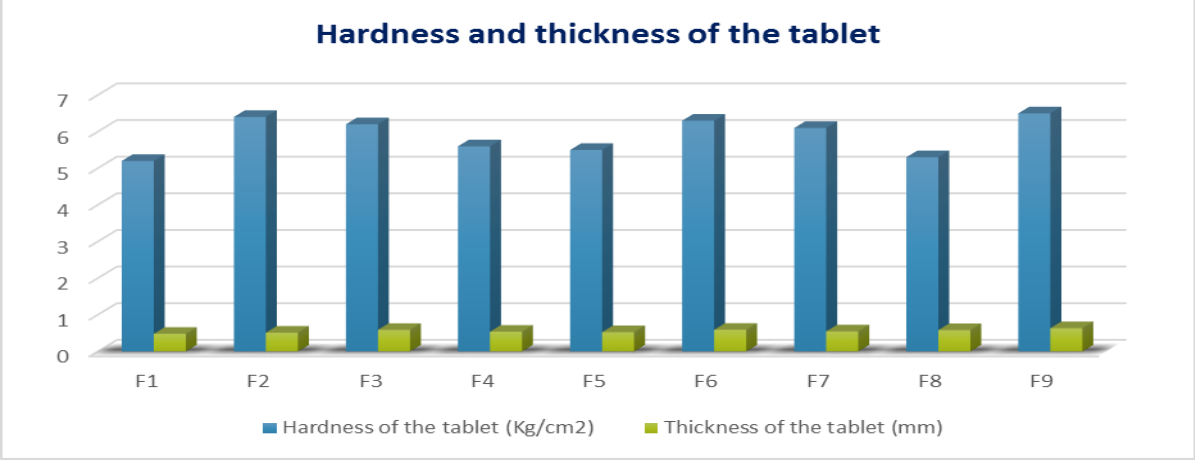


Fig .11: Figure of hardness and thickness

Friability test:

All the formulations exhibited less than 1% friability, which was within the limit, as shown in the table no.14.

Weight variation test:

The percentage weight variation for all formulations was performed.

The formulation is within limits, as shown in the table no.14.

Drug content:

The content uniformity test for montelukast sodium osmotic core tablet was performed. The results are found to be 96.08±0.57 -98.99±0.87 %. The results were found to be within the USP specification limits (90% -110%). It shows that the drugs are distributed uniformly.

Table no.14: Post formulation study results for core tablets

*** Mean SD (n = 3)**

Formulation code	Friability test (%)	Weight variation test(mg)	Drug content(%)
F1	0.537±0.03	0.193±0.88	96.25±0.45
F2	0.505±0.07	0.190±0.57	95.45±0.92
F3	0.462±0.05	0.195±0.24	96.88±0.58
F4	0.548±0.07	0.192±0.27	98.10±0.77
F5	0.515±0.04	0.203±0.47	96.08±0.57
F6	0.487±0.06	0.190±0.56	97.74±0.36
F7	0.492±0.05	0.190±0.79	98.11±0.95
F8	0.569±0.02	0.192±0.62	98.99±.0.87
F9	0.482±0.04	0.185±0.36	97.23±0.34

EVALUATION TEST OF MONTELUKAST SODIUM OSMOTIC COATED TABLETS

Montelukast sodium osmotic coated tablets were evaluated for various physical parameters namely thickness, hardness, friability, weight variation and uniformity of drug content and swelling study.

Table no.15: Post Formulation study results for coated tablets

Formulation code	Hardness test(Kg/cm^2)	Thickness(mm)	Weight variation test (mg)
F1C1	5.2±0.52	0.482±0.01	0.250±0.85
FC2	6.4±0.75	0.513±0.03	0.225±0.35
F3C3	6.2±0.46	0.588±0.01	0.220±0.64
F4C1	5.6±0.54	0.539±0.04	0.258±0.28
F5C2	5.5±0.66	0.526±0.02	0.260±0.45
F6C3	6.3±0.89	0.591±0.01	0.230±0.68
F7C1	6.1±0.73	0.547±0.03	0.247±0.39
F8C2	5.3±0.36	0.582±0.02	0.252±0.78
F9C3	6.5±0.87	0.634±0.01	0.233±0.25

*** Mean SD (n = 3)**

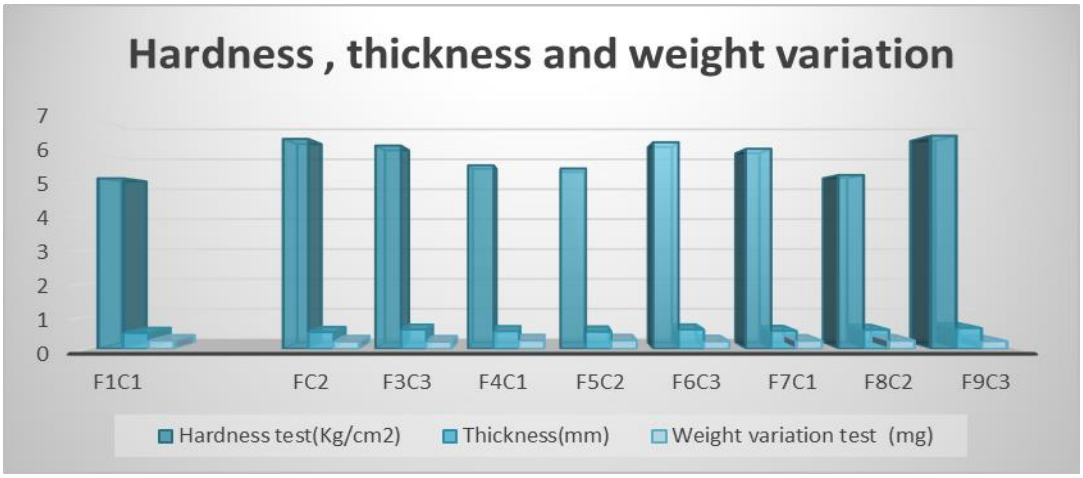


Fig 12: Figure of hardness, thickness and weight variation test

Table no.16: Friability and drug content results

Formulation code	Friability%	Drug content %
F1C1	0.64±0.02	98.24±0.45
F2C2	0.61±0.01	99.32±0.86
F3C3	0.54±0.04	98.45±0.79
F4C1	0.65±0.03	99.74±0.36
F5C2	0.62±0.01	97.36±0.74
F6C3	0.59±0.02	98.20±0.48
F7C1	0.59±0.02	98.22±0.97
F8C2	0.68±0.01	99.85±0.52
F9C3	0.58±0.04	98.17±0.42

***Mean SD (n = 3)**

Friability test:

All the formulations exhibited less than 1% friability, which was within limit, as shown in the table no.15.

Weight variation test:

The percentage weight variation for all formulations is performed.

The formulation is within limits, as shown in the table no.15.

Drug content:

The content uniformity test for montelukast sodium osmotic core tablet was performed. The results were found to be 97.36±0.74 -99.89±0.52 %. The results were found to be within the USP specification limits (90% -110%). It shows that the drugs are distributed uniformly.

Swelling study

The swelling study of the osmotic tablet is shown in table 17.

Table no.17: Results of swelling index

Formulation code	Swelling index (%)
F1	153
F2	186
F3	195
F4	192
F5	259
F6	260
F7	276
F8	314
F9	151

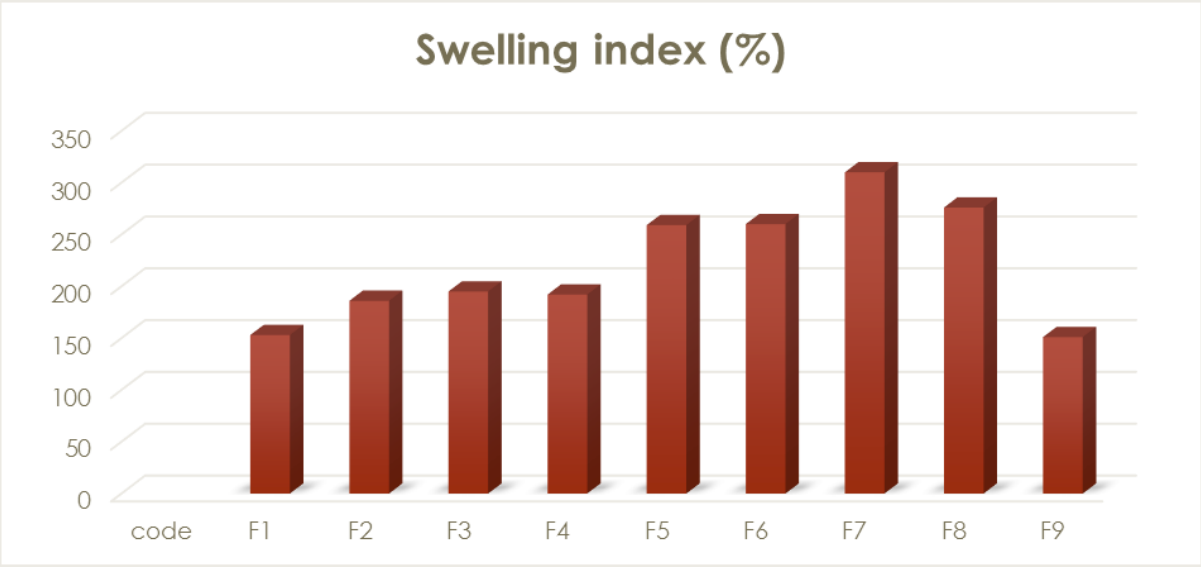


Fig .13: Figure of swelling index

***In-vitro* release study of the tablets**

The percentage of drug release from osmotic tablet were shown in table 18.

Table no.18: *In-vitro* study results

Time (hrs)	F1C1	F2C2	F3C3	F4C1	F5C2	F6C3	F7C1	F8C2	F9C3
1	13.25± 0.09	12.32± 0.12	13.42± 0.02	11.11± 0.24	12.10± 0.18	12.10± 0.75	16.67± 1.23	13.17± 0.19	17.07± 0.52
2	26.51± 0.95	27.21± 1.68	26.82± 0.38	23.28± 0.71	23.28± 0.78	27.06± 0.55	29.06± 0.29	29.96± 0.78	28.81± 0.23
3	37.13± 0.43	33.65± 1.73	31.17± 1.05	28.09± 1.57	28.09± 0.23	35.26± 0.72	41.20± 0.89	42.83± 0.68	43.17± 0.78
4	41.13± 0.13	46.21± 0.51	54.72± 0.14	37.70± 0.45	37.70± 0.75	43.19± 1.55	52.17± 0.54	58.96± 0.98	55.26± 0.17
5	62.12± 1.24	56.32± 0.86	64.72± 0.87	52.13± 1.04	52.13± 1.88	56.32± 1.67	69.01± 0.77	69.56± 0.22	61.67± 0.78
6	73.78± 0.96	72.13± 0.20	81.21± 0.19	61.17± 0.45	78.17± 0.78	69.21± 0.78	72.78± 1.54	85.96± 0.19	73.78± 0.36
7	81.95± 0.41	79.13± 1.98	85.17± 1.66	70.09± 0.45	86.09± 0.86	78.09± 1.26	86.29± 1.26	91.51± 0.89	83.95± 0.54
8	89.62± 0.13	90.32± 0.78	88.46± 0.57	90.12± 0.86	92.01± 0.57	90.45± 0.35	89.86± 1.45	94.99± 0.28	88.82± 0.77

***Mean SD (n = 3)**

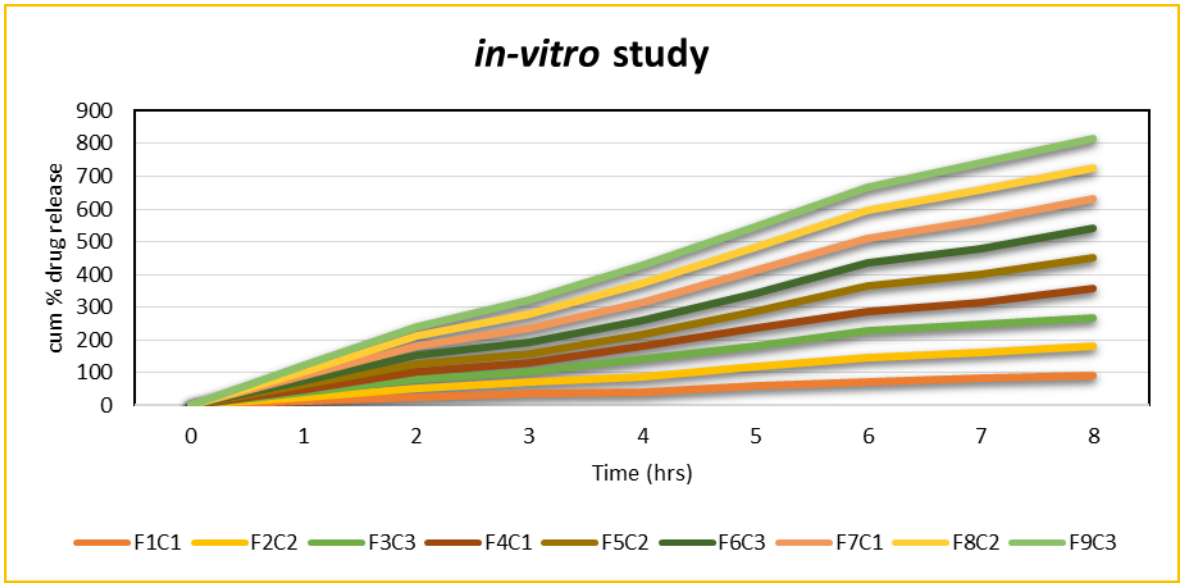


Fig.14: Results of *in-vitro* study

EVALUATION OF OPTIMIZED FORMULATION

Effect of amount of osmogen on drug release

To evaluate the effect of osmogen on drug release, the formulations were prepared with different concentrations of osmogens (mannitol, NaCl and lactose). The drug is released more readily when mannitol and sodium chloride concentration is raised.

This is due to an increase in osmogen concentration that raises the osmotic pressure within the tablet and speeds up the release of the drugs. The formulation F8C2 of has high concentration of mannitol and sodium chloride has shown the best release.

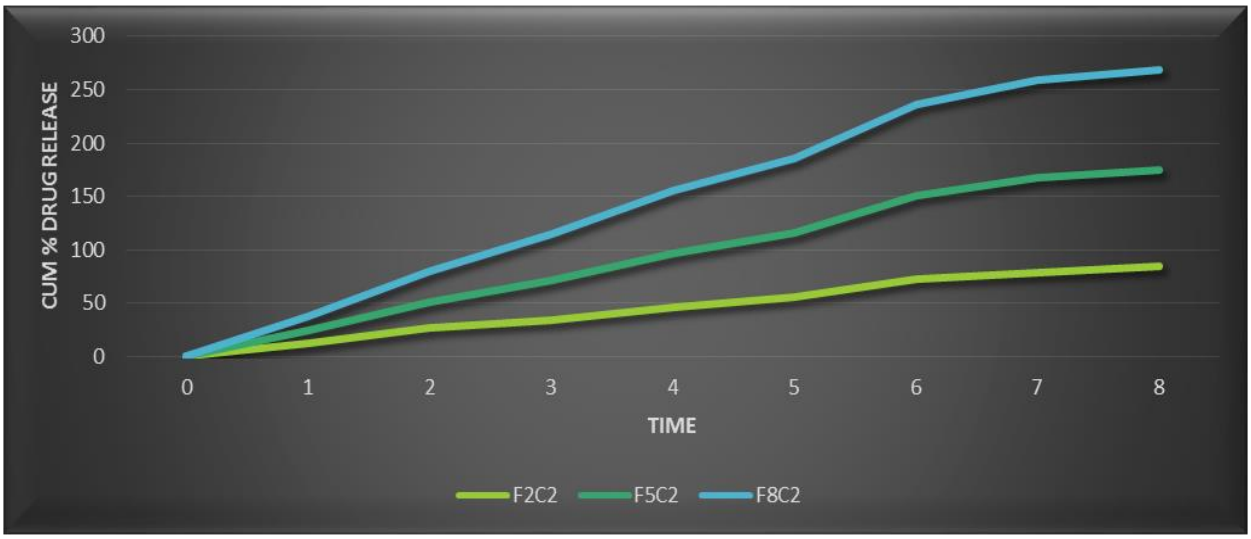


Fig. 15: Figure of effect of amount of osmogen

Effect of pore former on drug release

To evaluate the effect of pore former, SLS is used as pore former in different concentrations of 1%, 2% and 8%. The Drug release through pores, hence pore former concentration in controlled porosity osmotic tablets is an essential consideration in controlling the drug release. Drug release was reduced by a reduction in pore former concentration, while drug release was gradually raised by an increase in pore former concentration. The formulation F8C2 of 2 % of SLS has shown the controlled delivery of drug for 8 hrs.

Effect of agitation rates on drug release

To evaluate the effect of agitation on drug release, the optimized formulation F8C2 were exposed to different medium for dissolution of 8 hours.

The amount of drugs released is not greatly influenced by rotational speed. Consequently, the gastrointestinal tract motility may not significantly alter the release of drugs.

Table no.19: Effect of agitation rates on drug release results

Time (hrs)	**Rotational speed of the paddle**		
	Cumulative % of drug release		
	50 Rpm	**100 Rpm**	**150 Rpm**
1	13.02±0.12	13.17±1.05	13.21±0.41
2	29.25±0.56	29.96±0.57	29.50±1.24
3	42.15±0.27	42.83±0.95	42.30±1.87
4	58.42±0.35	58.96±0.45	58.88±0.21
5	69.42±0.78	69.56±1.24	69.45±1.66
6	85.32±0.88	85.96±0.77	85.55±0.23
7	91.32±1.20	91.51±1.08	9.36±0.14
8	94.55±0.87	94.99±0.13	94.89±0.98

***Mean SD (n = 3)**

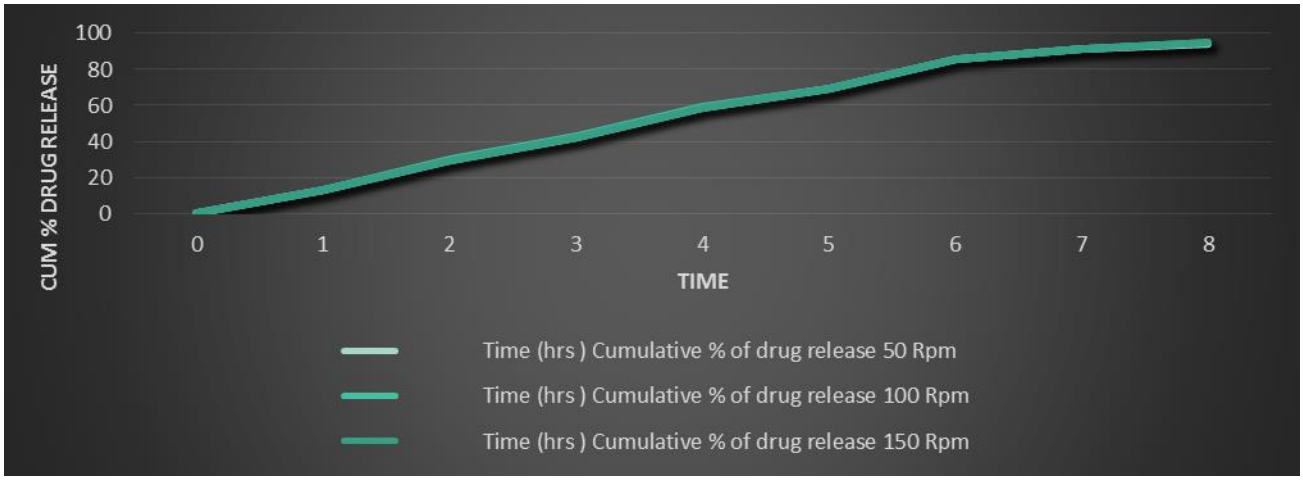


Fig .16, Figure of effect of agitational rates

Effect of coat thickness on drug release

To evaluate the coat thickness of tablet the montelukast sodium osmotic tablet is coated with different percentages of 3%, 6% and 9%. Drug release was decreased with increase in coat thickness of semipermeable membrane. The decrease in the coat thickness resulted in increased drug release. The formulation F8C2 and F5C2 resulted in controlled delivery of drugs.

Effect of pH on drug release

The optimised formulation F8C2 was tested for drug release in various dissolution media of 0.1N HCL pH 1.2, phosphate buffer pH 6.8, and phosphate buffer pH 7.2, in order to determine the impact of pH on drug release.

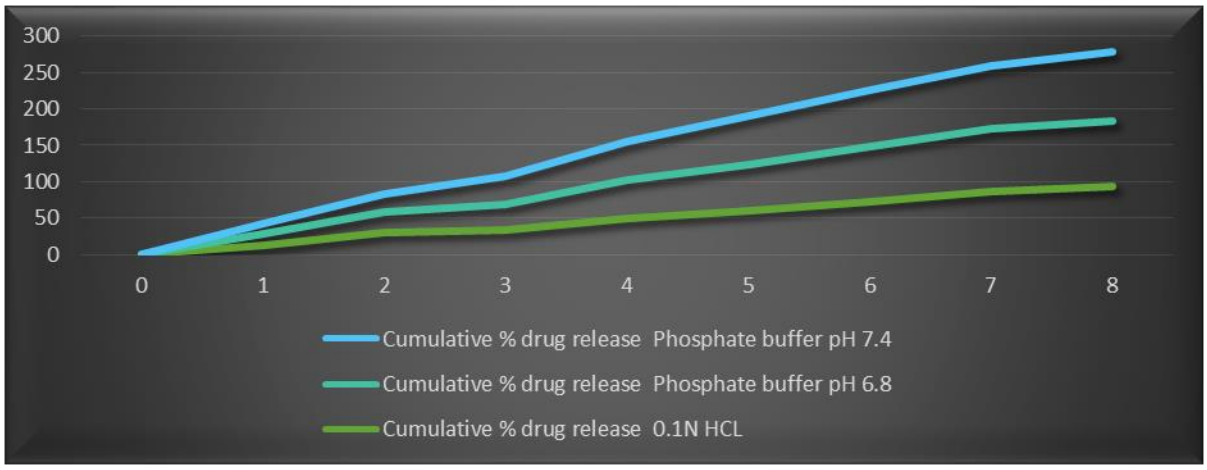


Fig. 17: Figure of effect of pH results

Table no.20: Effect of pH on drug release

Time (hrs)	Cumulative % drug release		
	0.1N HCL	**Phosphate buffer pH 6.8**	**Phosphate buffer pH 7.4**
1	13.33±1.84	15.23±1.06	13.89±1.20
2	29.54±0.27	28.87±1.27	29.45±1.63
3	33.87±0.20	32.04±0.46	35.17±0.85
4	50.02±0.63	51.73±0.19	54.23±0.17
5	60.42±0.15	63.54±0.87	67.23±0.32
6	72.02±1.08	76.23±0.54	78.20±0.46
7	86.55±0.79	86.09±0.21	86.20±0.79
8	92.76±0.71	90.34±0.78	94.87±0.74

***Mean SD (n = 3)**

The amount of drugs released was not greatly influenced by effect of pH. Consequently, the gastrointestinal tract motility may not significantly alter the release of drugs. There was the best effect on pH 7.4 of phosphate buffer.

Membrane Morphology of porous montelukast sodium Osmotic Tablet

From SEM analysis the tablet surface morphology was obtained before and after dissolution. Membranes obtained before dissolution revealed a non-porous zone. After 8 hours of dissolution, the membrane displayed pore creation as a result of SLS eroding from the membrane, causing the drug release. In comparison to formulation F8 coated with coating

solution C3 containing 4% SLS and coating solution C2 containing 2% sorbitol created fewer pores.

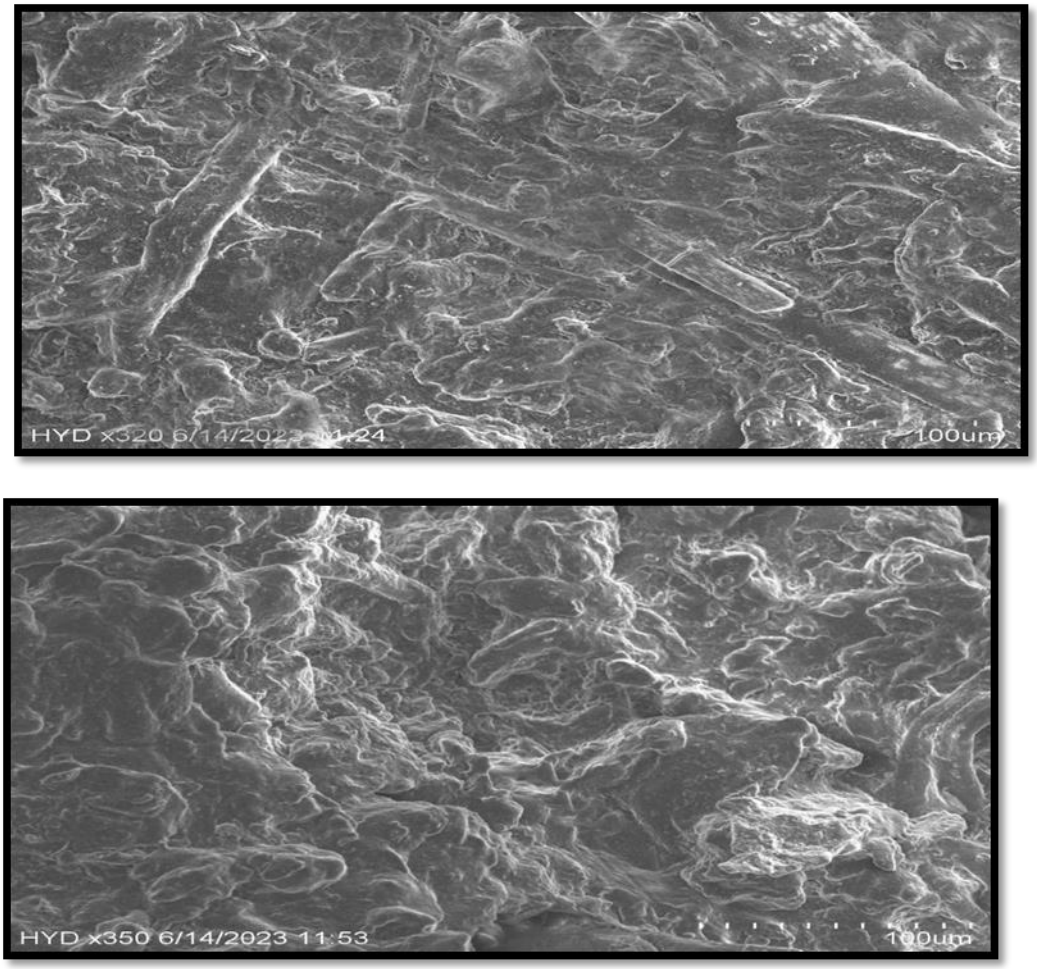
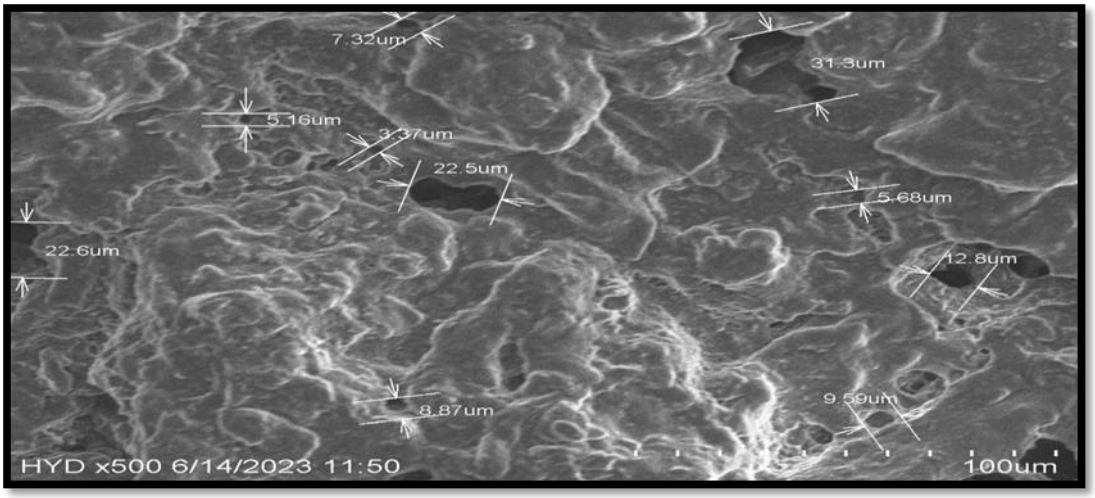


Fig.18: Membrane morphology of F8C2 before dissolution



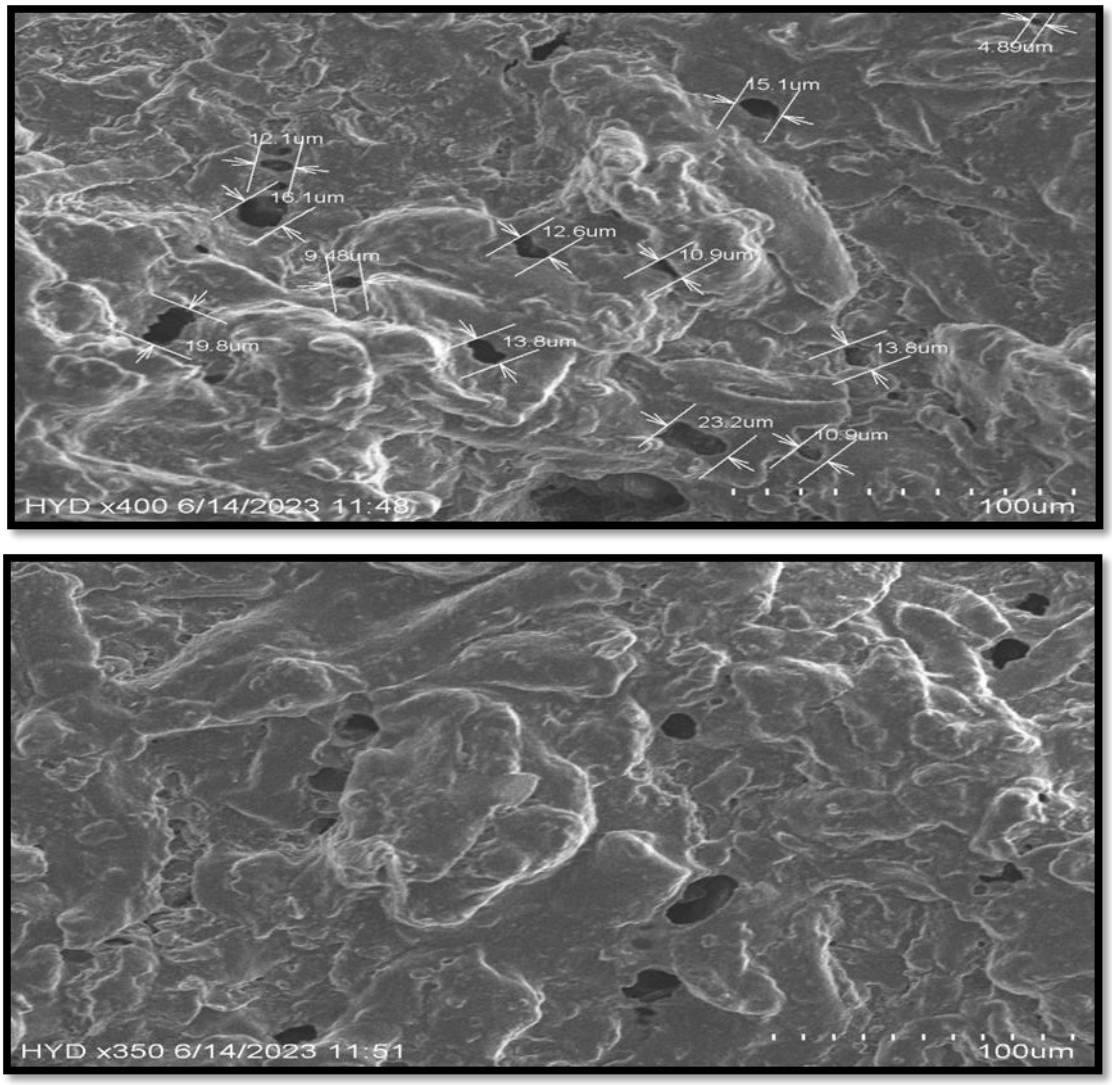


Fig.19: Membrane morphology of F8C2 after dissolution

9.8. DRUG RELEASE KINETIC STUDY:

The in-vitro release data obtained for the formulation was subjected to kinetic analysis. The cumulative % drug release data were fitted into zero order, first order, Higuchi's square root, Korsmeyer Peppas equation, and Hixson Crowell equation. The results are given in the table.

Table no.21*: In-vitro* release kinetics of optimized formulation

Time(hrs)	log time	sq. root of time	cum% drug release	Cum % drug remaining	log cum % drug release	log cum % drug remaining	cube root of cum % remaining
1	0	1	13.17	86.83	1.119585775	1.938669801	4.428159617
2	0.30103	1.414213562	29.96	70.04	1.476541809	1.845346137	4.122070157
3	0.47712	1.732050808	42.83	57.17	1.631748074	1.757168192	3.852323329
4	0.60206	2	58.96	41.04	1.770557475	1.613207352	3.449338247
5	0.69897	2.236067977	69.56	30.44	1.842359573	1.483444648	3.122349753
6	0.77815	2.449489743	85.96	14.04	1.934296407	1.147367108	2.412435455
7	0.8451	2.645751311	91.51	8.49	1.961468555	0.92890769	2.040026912
8	0.90309	2.828427125	94.99	5.01	1.977677888	0.699837726	1.711115171

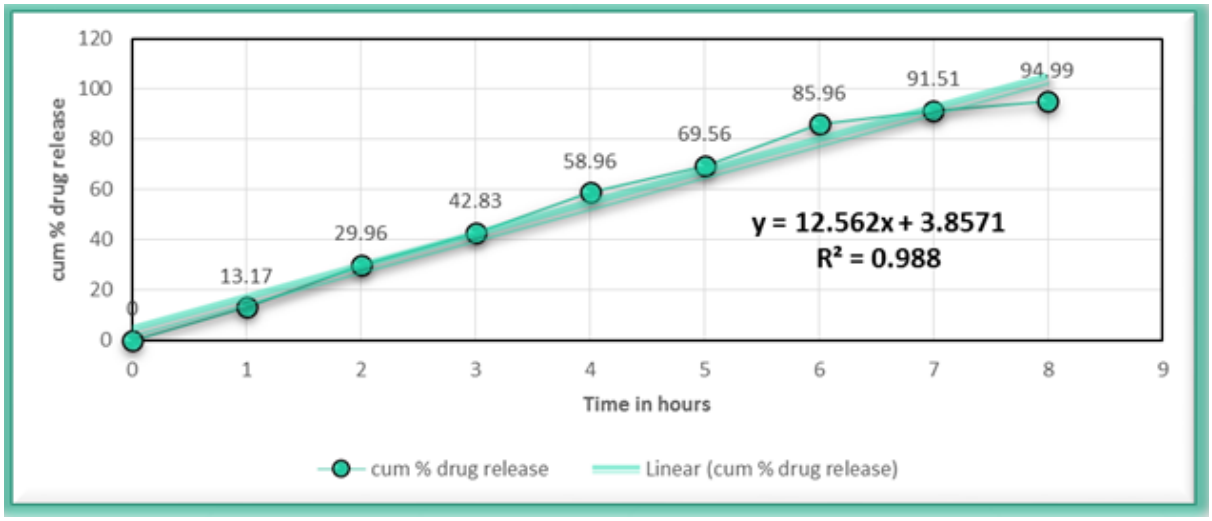


Fig. no: 20 Plot for zero order kinetics

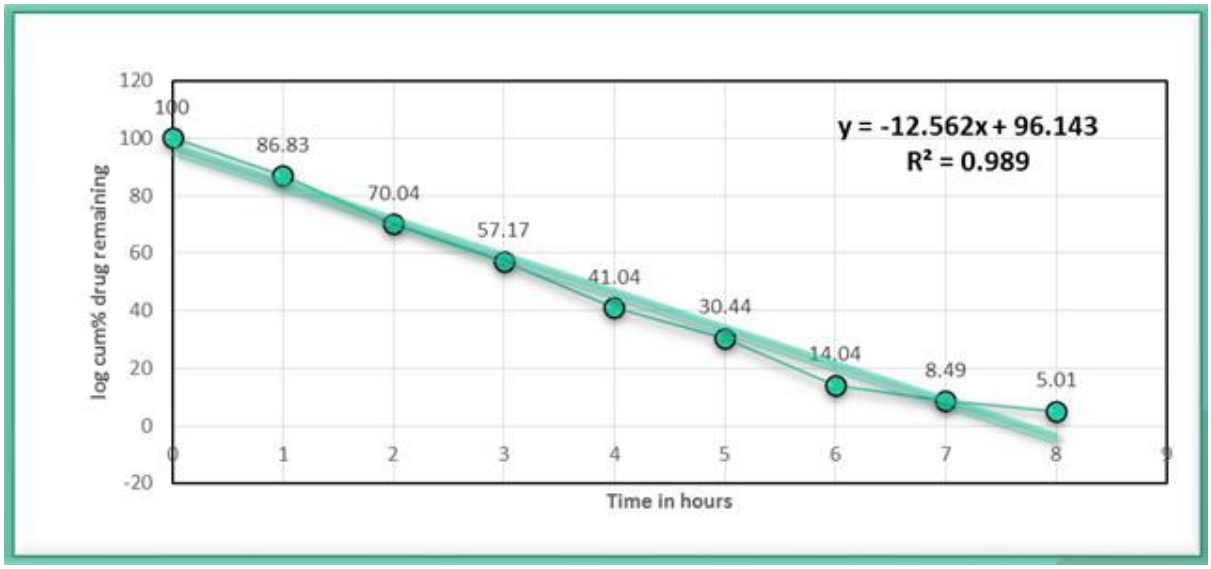


Fig. no:21 Plot for first order kinetics

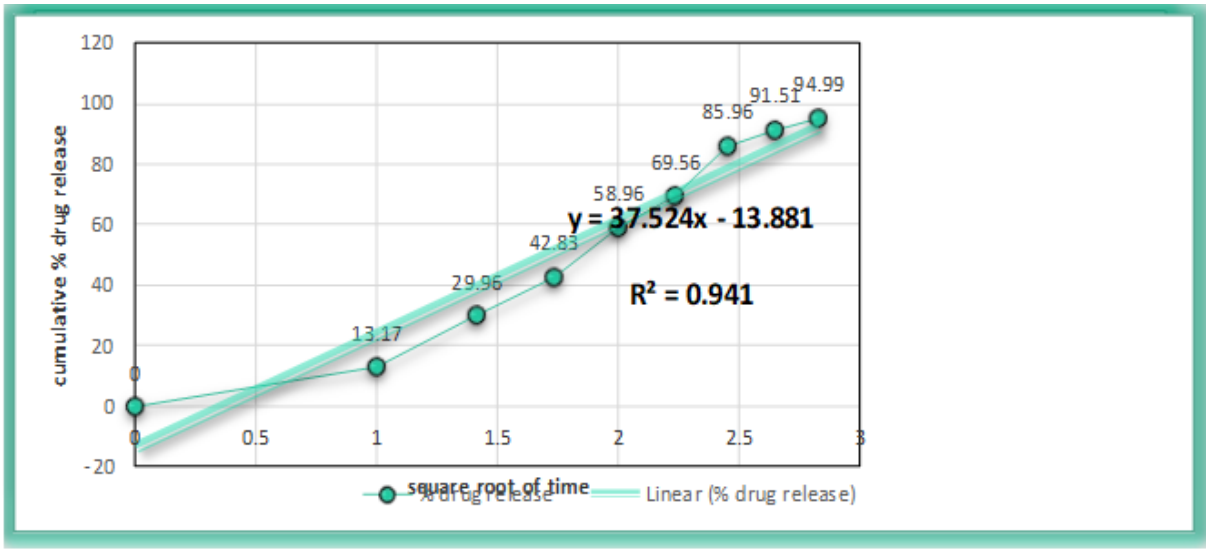


Fig.no:22 Plot of Higuchi kinetics

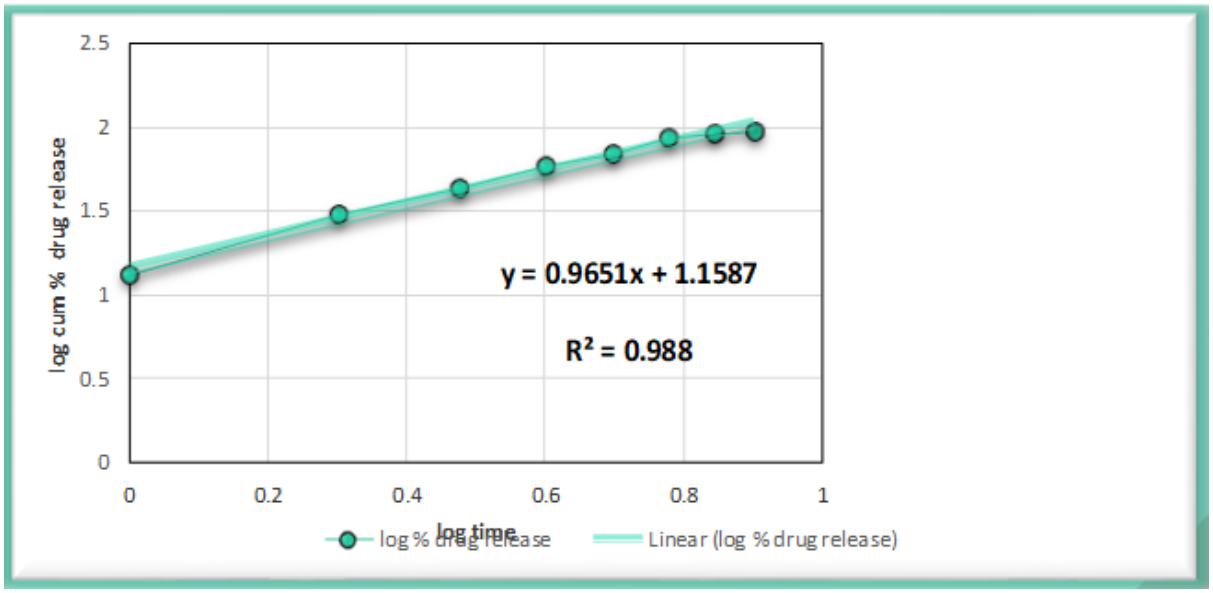


Fig.no:23 Plot of Korsmeyer and Peppas Kinetics

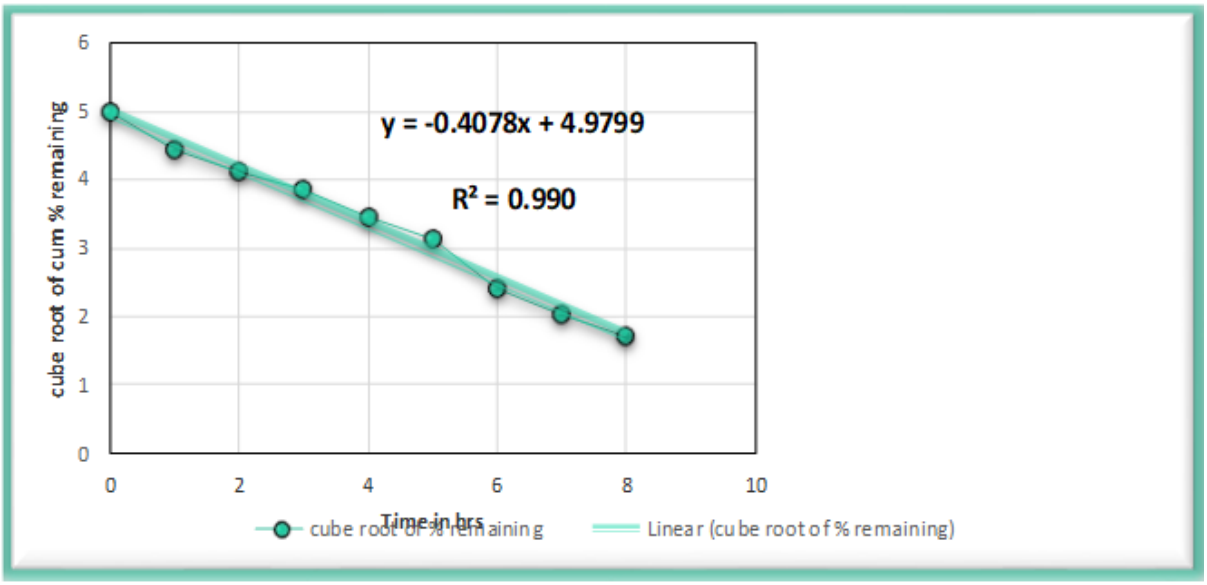


Fig.no:24 Plot of Hixson – Crowell kinetics

The coefficient of determination (R2) was taken as criterion for choosing the appropriate model. The R2 values of various models are in table.no:22

Table no :22 R2 values for various kinetics model coefficient of determination R2

KINETIC MODEL	COEFFICIENT OF DETERMINATION (R2)
Zero-order kinetics	0.989
First order kinetics	0.988
Higuchi kinetics	0.941
Korsmeyer and Peppas Kinetics	0.988
Hixson – Crowell kinetics	0.990

The in vitro drug release of the optimized formulation F8C2 was best explained by Hixson Crowell as the plots showed the highest linearity (R2=0.990**)** followed by zero-order (R2=0.989).

Stability studies

Stability studies were carried out of the optimized formulation at 40ºC ± 2ºC & 75 % ± 5 % RH for three months as per ICH guidelines. At various time intervals (initial, 1st month, 2nd month and 3rd month), samples were evaluated for appearance, average weight (mg), Hardness etc. There was no major change in the evaluation parameters. The results are shown in Table 23.

Table no.23: Stability study results

S.no.	Parameters Tested	Storage conditions	
		Initial **1st month**	**Final** **3rd month**
1	Description	Yellow round concave tablets	No change
2	Average weight (mg)	190±0.53	190±0.62
3	Drug content	98%±0.71	98%±0.49
4	Hardness (Kp)	6.2±0.88	6.2±0.92
5	Friability (%)	0.68±0.03	0.68±0.01

CONCLUSION

In the present study, an attempt has been made to develop an osmotic drug delivery system in the form of a tablet for the release of montelukast sodium in a unidirectional manner with improved bioavailability.

From the results obtained in the present study, it can be concluded that:

Fourier transform infrared spectroscopic studies showed no significant Drug–excipient interaction. So, it can be concluded that drug and other excipients are compatible with each other.

The formulated tablets were satisfactory in terms of physical parameters (hardness, thickness, weight variation), drug content, swelling index, and *in- vitro* drug release.

Although all osmotic tablets exhibited satisfactory drug release, the best results were obtained with tablet of Formulation F8C2.

In vitro dissolution studies of the optimized formulation indicated the drug release followed Zero Order Kinetics.

In controlled porosity osmotic system, core tablets are coated with a semipermeable membrane having a pore former. After coming in contact with aqueous media, pore dissolves and leaches out from the coating that creates pores in surface of the tablet and the drug is releases through the pores.

The above study demonstrated the possibility of making an osmotic drug delivery system for montelukast sodium which will be more efficacious and acceptable than the conventional drug delivery of montelukast sodium and it could be a drug delivery of choice in the treatment of Asthma.

ACKNOWLEDGEMET

The authors are very thankful to the principal and management of K.K. College of Pharmacy, for providing necessary facilities to carry out this work.

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