"DEVELOPMENT AND OPTIMIZATION OF METFORMIN HYDROCHLORIDE SUSTAINED RELEASE TABLETS"

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy

BY

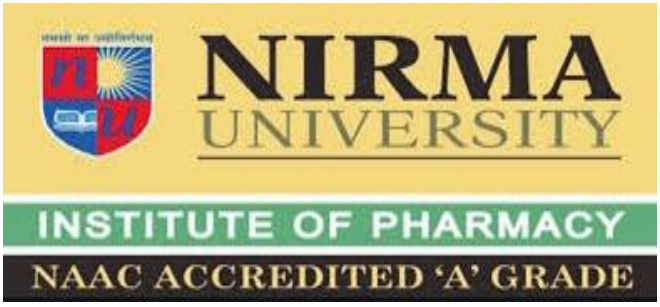
PATEL PARIN R. (16BPH066)

Semester VIII

UNDER THE GUIDANCE OF

DR. BHUMIKA D. PATEL (Guide)

DR. TEJAL MEHTA (Co-guide)



INSTITUTE OF PHARMACY

NIRMA UNIVERSITY

SARKHEJ-GANDHINAGAR HIGHWAY

AHMEDABAD-382481

GUJARAT, INDIA

MAY 2020

CERTIFICATE

This is to certify that **"DEVELOPMENT AND OPTIMIZATION OF METFORMIN HYDROCHLORIDESUSTAINED RELEASE TABLETS"** is the bonafide work carried out by**PATEL PARIN (16BPH066)**, B.Pharm semester VIII under our guidanceand supervision in the Institute of Pharmacy, Nirma University, Ahmedabadduring the academic year 2019-2020. This work is up to my satisfaction.

Guide:

Dr. Bhumika D. Patel
M.Pharm., Ph.D.,
Assistant professor,
Department of Pharmaceutical chemistry,
Institute of Pharmacy,
Nirma University

Co-Guide:

Dr. Tejal Mehta
M.Pharm., Ph.D.,
Head, Department of
Pharmaceutics,
Institute of Pharmacy,
Nirma University

Dr. Hardik Bhatt
M.Pharm., Ph.D.,
Head, Department of Pharmaceutical chemistry,
Institute of pharmacy,
Nirma University

Prof. Manjunath Ghate
M.Pharm., Ph.D.,
Director,
Institute of Pharmacy,
Nirma University

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Patel Parin (16BPH066)
Institute of Pharmacy,
Nirma University
Sarkhej-Gandhinagar Highway,
Ahmedabad-382481
Gujarat, India

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Institute of Pharmacy,
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Nirma University

DECLARATION

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Patel Parin (16BPH066)
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Nirma University
Sarkhej-Gandhinagar Highway,
Ahmedabad-382481
Gujarat, India

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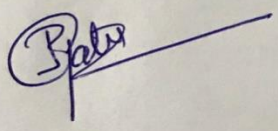

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ABSTRACT:

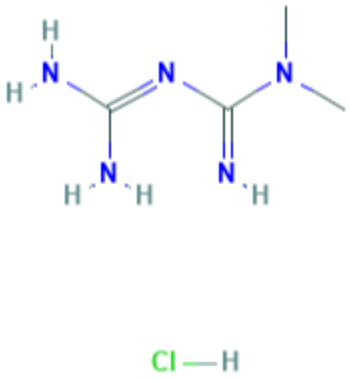
The objective of this study was to compare natural and synthetic polymers to develop metformin hydrochloride sustained release matrix tablet. Polyox WSR-301, HPMC K100M, Eudragit L100 were taken as synthetic polymers while Guar gum, Xanthan gum and sodium alginate were taken as natural polymers. Matrix tablets containing 250mg metformin hydrochloride and polymers in different ratio (1:0.5, 1:1, 1:2) were produced by direct compression and optimized using pre-compression and post-compression parameters such as angle of repose, Carr's index, Hauner's ratio, hardness, friability, weight variation, drug content and *in-vitro* drug release. From the results obtained *by in-vitro* drug release profile, it was concluded that Polyox WSR-301, HPMC K100M, Eudragit L100 offered desired results at low ratios of 1:0.5, 1:1 and 1:0.5 respectively, while Xanthan gum and sodium alginate at ratio of 1:2 and guar gum failed to offer required drug release as per USP i.e 85% drug release in 12 hrs

1. INTRODUCTION:

The rationale of this study is to formulate metformin hydrochloride sustained release tablet. Patients suffering from type II diabetes have to take medication throughout their life span to control the blood glucose levels.There are plenty of oral anti-hyperglycemic agents in the market and metformin is the first choice of drug for the patients having type II diabetes, especially for overweight patients. Metformin minimizes glucose production in liver, decreases glucose absorption from intestine and enhance sensitivity of insulin by enhancing peripheral uptake and utilization of glucose. Such medications require higher patient compliance so as to achieve desire goal. This experiment focuses on the screening of different polymers to formulate a cost effective sustained release tablet. From the results of the experiment one can find the polymer which works on minimum concentration and can be chosen to develop a desired sustained release product.

(Corti et al., 2008)

Metformin is a water soluble drug, having 50-60% absolute bioavailability. This property of metformin allows oral administration. Major obstacle for developing an oral formulation is that metformin has comparatively short plasma half-life of 1.5-4.5 hrs. This leads to frequent administration of large dose and by doing so; it may cause severe gastrointestinal discomfort. So to overcome that, a sustained released formulation can be developed, which can minimize the dose frequency.



[Metformin hydrochloride]

'Sustained release' formulations are generally prepared to impart a prolong action of drug by maintaining the plasma concentration at the therapeutic level for long duration. Sustained release formulations are meant to release the active ingredient at predetermined and controlled manner. Thus, sustained release formulations are prepared to minimize the dose frequency. By lowering the dose frequency more patient compliance can be achieved. In addition to that, sustained release formulations minimize the adverse drug reactions as well.

Diabetes mellitus occurs when there is insufficient secretion of insulin by the pancreas or may be due to resistance of insulin which leads to increased blood glucose level. Almost 400 million cases have been identified around the world, which might be expected to rise around 472 million by 2030.

In this study different polymers were tested for formulation of metformin sustained release tablets. Polyox is a homopolymer having long chain of eyhylene oxide. The major advantage of polyox for a sustained release formutaion is that it shows quick hydration and forms stable gel which is independent of Ph. In addition to that it has greate versatility in direct compression and granulation. Wide range of grades shows different properties like viscoelastisity, film forming, thickening, timed release etc. Here, polyox WSR301 is selected having molecular weight around 4,000,000 which is suitable for the timed release formulations.

[Polyox (polyethyleneoxide)]

(Shah et al., 2014)

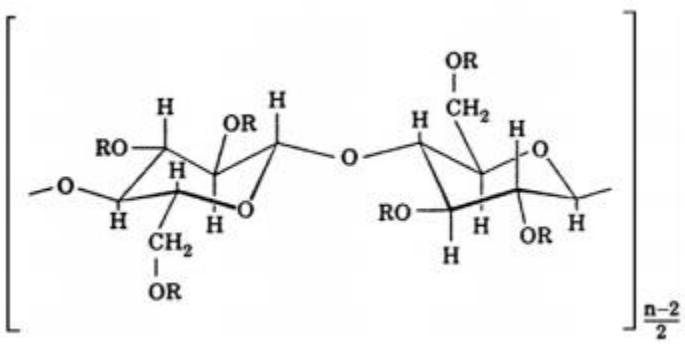
Eudragits are copolymers of methyl methacrylate, ethyl acrylate and methacrylic acid ester linked to the quaternary ammonium moiety. Different grades of eudragit are used to develop sustained release formulations, site targeted formulations or controlled release

formulation. The major properties of eudragit is that it has high degree of swelling which is independent of Ph. Here, eudregit L100 is chosen to impart desired release retardation.

[methacrylic acid] [Ethyl acrylate]

(Singh et al., 2015)

HPMC (Hydroxypropyl methylcellulose), also known as hypromellose is a semi synthetic derivative of cellulose and it is widely used in oral controlled release formulations. HPMC has good swelling property when it comes in contact with biological fluids. There are varieties of grades of HPMC and for this study HPMC K100M is taken as the polymer to obtain the sustained release of the metformin.



[HPMC (HydroxyPropyl MethylCellulose)]

Natural gums have been used in the novel drug delivery systems. Natural polymers are biodegradable and easily available. In addition to that natural polymers are cost-effective and environment friendly. So, use of natural polymers in the sustained release formulation may impart the desired property in low cost.

Guar gum comes under the category of gallactomannans and also known as guaran. It is extracted from the guar beans. Xanthan gum is produced by micro-organisms 'Xanthomonas campestis' as an extra cellular polysaccharide. Sodiumalginate is obtained as a sodium salt form of alginic acid and present in the cell wall of brown algae.

(Košir et al., 2018),(Wadher et al., 2011),(Fukuda et al., 2006),(Khullar et al., 1998)

In this experiment metformin HCl tablets were produced by direct compression method and various evaluation parameters were checked for each batch. Every polymer was taken in different ratios (1:0.5, 1:1, 1:2) and total 18 batches were prepared. Powder blends were checked for some pre-compression tests such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. Results of these tests give idea about the flow property of the powder blends. After compressing the tablets, all the batches were subjected to post-compression tests like hardness, thickness, weight variation, content uniformity and in-vitro drug release test. *In-vitro* drug release test is the crucial parameter for sustained release formulation. Based on the results of *in-vitro* drug release test, optimum concentrations of different polymers were selected. Synthetic polymers were compared with the natural polymers and conclusion of the experiment was made.
(Upadhyay et al., 2014),(Nikam, 2011)(Barzegar-Jalali et al., 2013)

2. MATERIALS AND METHODS:

2.1 Material:

Metformin hydrochloride, Polyox WSR-301, HPMC K100M, Eudragit L100, Guar gum, Xanthan gum, sodium alginate, PVP K30, Lactose, Starch, Talc, Magnesium stearate, 0.1 N HCl, Phosphate buffer of pH 6.8.

2.2 Procedure:

Preparation of matrix tablets containing metformin HCl:

As the quantity specified in table 1 and 2, Metformin HCl, lactose, PVP K30 and starch was weighed accurately and transferred to a mortar.WSR-301 / HPMC K100M / Eudragit L100 / Guar gum / Xanthan gum / sodium alginate in different ratio (1:0.5/ 1:1/ 1:2) was added to the blend and triturated for 20 minutes. Magnesium stearate and talc were added and mixture was further triturated for another 20 minutes. Prepared mixtures were compressed in a rotary tablet punching machine and tablets weighing around 1000 mg were obtained.

[Table 1.Composition table]

INGREDIENT	SP1	SP2	SP3	SE1	SE2	SE3	SH1	SH2	SH3
Metfomin HCl (mg)	250	250	250	250	250	250	250	250	250
Lactose (mg)	525	400	150	525	400	150	525	400	150
PVP (mg)	20	20	20	20	20	20	20	20	20
Starch (mg)	70	70	70	70	70	70	70	70	70
Polyox WSR-301(mg)	125	250	500	0	0	0	0	0	0
Eudragit L100(mg)	0	0	0	125	250	500	0	0	0
HPMC K100M(mg)	0	0	0	0	0	0	125	250	500
Guar gum (mg)	0	0	0	0	0	0	0	0	0
Xanthan gum (mg)	0	0	0	0	0	0	0	0	0
Sodium alginate (mg)	0	0	0	0	0	0	0	0	0
Mg stearate (mg)	5	5	5	5	5	5	5	5	5
Talc (mg)	5	5	5	5	5	5	5	5	5
Total (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000

[SP1: Synthetic Polyox (1:0.5), SP2: Synthetic Polyox(1:1), SP3: Synthetic Polyox (1:2),SE1: Synthetic Euragit (1:0.5), SE2: Synthetic Eudragit (1:1), SE3: Synthetic Eudragit (1:2), SH1: Synthetic HPMC (1:0.5), SH2: Synthetic HPMC (1:1), SH3: Synthetic HPMC (1:2),Metformin HCL: Metformin hydrochloride, PVP: Polyvinylpyrrolidone, HPMC: Hydroxypropylmetylcellulose , Mg Stearate: Magnesium stearate]

[Table 2.Composition table]

INGREDIENT	NG1	NG2	NG3	NX1	NX2	NX3	NS1	NS2	NS3
METFORMIN HCl (mg)	250	250	250	250	250	250	250	250	250
Lectose (mg)	525	400	150	525	400	150	525	400	150
PVP (mg)	20	20	20	20	20	20	20	20	20
Starch (mg)	70	70	70	70	70	70	70	70	70
Polyox (mg)	0	0	0	0	0	0	0	0	0
Eudragit (mg)	0	0	0	0	0	0	0	0	0
HPMC (mg)	0	0	0	0	0	0	0	0	0
Guar gum (mg)	125	250	500	0	0	0	0	0	0
Xanthan gum (mg)	0	0	0	125	250	500	0	0	0
Sodium alginate (mg)	0	0	0	0	0	0	125	250	500
Magnesium stearate (mg)	5	5	5	5	5	5	5	5	5
Talc (mg)	5	5	5	5	5	5	5	5	5
Total (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000

[NG1: Natural Guargum (1:0.5), NG2: Natural Guargum (1:1), NG3: Natural Guargum (1:2), NX1: Natural Xanthangum (1:0.5), NX2: Natural Xanthangum (1:1), NX3: Natural Xanthangum (1:2), NS1: Natural Sodiumalginate (1:0.5), NS2: Natural Sodiumalginate (1:1), NS3: Natural Sodiumalginate (1:2),Metformin HCL: Metformin hydrochloride, PVP: Polyvinylpyrrolidone, HPMC: Hydroxypropylmetylcellulose , Mg Stearate: Magnesium stearate]

3. EVALUATION:

3.1 Pre-compression Tests:

3.1.1 Angle of repose:

Maximum possible angle between the surface of pile of powder and horizontal height of the pile is termed as angle of repose. Here, every powder blend was checked for the angle of repose using funnel method. Powder mixture was allowed to drop through the orifice of the funnel. A pile was formed on a plane paper kept below the funnel. Radius and height of the pile was measured. Finally the angle of repose was determined by the equation 1.

$$tan\theta = \frac{h}{r} \text{(eq.1)}$$

3.1.2 Bulk density:

Bulk density is a ratio of weight of powder in gram and the volume of powder in cm^3. For this parameter 20 grams of powder mixture was allowed to flow in the calibrated cylinder. The volume was determined and bulk density was measured by the equation 2.

$$Bulkdensity = \frac{Bulkmass}{Bulkvolume} \qquad \text{(eq. 2)}$$

3.1.3 Tapped density:

Tapped density is a ratio of weight of powder in grams and tapped volume in cm^3. For this parameter 20 grams of powder blend was allowed to flow in a calibrated measuring cylinder. The cylinder was tapped on a flat surface for 100 times. The final tapped volume was measured and tapped density was determined by equation 3.

$$Tapped\ density = \frac{Bulk\ mass}{tapped\ volume} \qquad \text{(eq. 3)}$$

3.1.4 Carr's index:

Carr's index is the critical and most important parameter to check the flow property of the powder. Here, every powder mixture was checked for the Carr's index from the values of bulk density and tapped density. Carr's index was determined by given equation4.

$$Carr'index = \frac{(Tapped\ density - Bulk\ density)}{Tapped\ density} * 100 \qquad \text{(eq. 4)}$$

3.1.5 Hausner's ratio:

Hausner's ratio is expressed as tapped density divided by bulk density. It is an important parameter to decide the compressibility of the powder-blend. Every powder-blend was checked for the Hausner's ratio by given equation 5.s

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density} \qquad \text{(eq. 5)}$$

[Table 3.Pre-compression parameters]

BATCH	ANGLE OF REPOSE (Mean±SD)	BULK DENSITY (gm/cm^3)	TAPPED DENSITY (gm/cm^3)	CARR'S INDEX	HAUSNER'S RATIO
SP1	26.13±0.14	0.511	0.596	14.262	1.166
SP2	24.44±0.18	0.587	0.642	8.567	1.094
SP3	22.24±0.23	0.526	0.614	14.332	1.167
SE1	27.23±0.10	0.695	0.753	7.703	1.083
SE2	25.52±0.02	0.635	0.765	16.993	1.205
SE3	22.19±0.21	0.596	0.635	6.142	1.065
SH1	28.19±0.53	0.688	0.756	8.995	1.099
SH2	25.87±0.11	0.625	0.723	13.555	1.157
SH3	22.06±0.16	0.665	0.742	10.377	1.116
NG1	23.27±0.20	0.521	0.593	12.142	1.138
NG2	22.55±0.01	0.547	0.598	8.528	1.093
NG3	21.52±0.01	0.532	0.586	9.215	1.102
NX1	22.62±0.06	0.523	0.615	14.959	1.176
NX2	21.61±0.02	0.576	0.685	15.912	1.189
NX3	21.62±0.22	0.611	0.702	12.963	1.149
NS1	24.23±0.06	0.635	0.756	16.005	1.191
NS2	23.66±0.01	0.614	0.694	11.527	1.130
NS3	22.53±0.01	0.598	0.693	13.709	1.159

3.2 Post-compression Tests:

3.2.1 Hardness test

Hardness of the tablet should be optimum so that it can withstand the packaging and transportation. Here, three tablets from each composition were randomly taken and hardness was determined by Monsanto hardness tester. The average hardness for each blend was calculated along with standard deviation.

3.2.2 Thickness

Thickness of the tablets was measured by vernier caliper in millimeters. Three tablets were randomly chosen from each composition and average thickness was measured alongwith the standard deviation.

3.2.3 Friability test

Friability was checked for each batch of tablets. Roche friabilator was used to measure %friability. 10 tablets were accurately weighed (W1) and put into friabilator. Apparatus was rotated at 25 rpm for 4 minutes. Tablets were taken out and weighed again (W2) and %friability was calculated by given equation 6.

$$\%Fribility = \frac{W1-W2}{W1} * 100 \text{(eq. 6)}$$

3.2.4 Weight variation test

Weight variation test was performed for each batch of tablets. 10 tablets were weighed accurately and average weight was determined. The variation from average weight was determined as %weight variation by given equation 7.

$$\%Weight\ variation = \frac{Average\ weight-Individual\ weight}{average\ weight} * 100 \quad \text{(eq. 7)}$$

3.2.5 Content uniformity test:

Preparation of working standard solution:

Standard solution of metformin HCL was prepared to check the drug content. 10 mg metformin hydrochloride was accurately weighed and takeninto a volumetric flask having 100 ml capacity.70 ml of distilled water was incorporated and the solution was put into sonicator for 10 minutes. Volume was adjusted to the mark by distilled water. Solution was filtered and 10 ml of filtrate was further diluted to 100 ml by distilled water so, the concentration of resulting solution was 10 µg/ml.

Preparation of test solution:

Test solution was prepared for each tablet composition. 20 tablets were individually weighed and average weight was calculated. Tablet was triturated using a glass mortar and powder containing 100 mg of metformin HCl was weighed accurately. Powder was

takeninto a volumetric flask having 100 ml capacity and 70 ml distilled water was added. The solution was kept in thesonicator for 10 minutes. Solution was filtered and 1 ml of filtrate was taken and further diluted up to 100 ml by distilled water.

Determination of drug content

Standard and test solutions were checked for the absorbance by UV-Visible spectrophotometer at 232 nm wavelength and drug content was calculated by given equation 8 and equation. 9.

$$Amount\ of\ metformin = \frac{Test\ Absorbance}{Standard\ Absorbance} * \frac{standard\ dilution}{test\ dilution} * Average\ weight \quad \text{(eq. 8)}$$

$$\%Content = \frac{Amount\ present}{Label\ claim} * 100 \quad \text{(eq. 9)}$$

(Ashour & Kabbani, 2003)(Dange et al., 2017)

[Table 4.Post-compression test]

BATCH	HARDNESS (kg/cm^2)	THICKNESS (mm)	AVERAGE WEIGHT (mg)	% FRIABILITY	% DRUG CONTENT
SP1	4.56±0.16	4.24±0.16	1001.6±0.6	0.69	98.66±0.39
SP2	5.12±0.09	4.22±0.09	1005.7±0.9	0.52	99.54±0.09
SP3	5.66±0.12	4.23±0.12	1005.3±1.1	0.51	99.42±0.49
SE1	5.69±0.13	4.19±0.13	996.6±0.3	0.75	99.32±0.6
SE2	6.44±0.15	4.24±0.15	999.7±0.4	0.66	98.45±0.71
SE3	6.95±0.06	4.21±0.06	1001.6±0.6	0.48	100.2±0.42
SH1	5.36±0.09	4.24±0.09	1004±0.6	0.66	99.53±0.08
SH2	5.42±0.14	4.22±0.14	1001.6±1.2	0.62	99.41±1.06
SH3	6.17±0.13	4.21±0.13	999.6±0.6	0.69	101.63±0.96
NG1	3.23±0.12	4.23±0.12	996.5±0.5	0.84	101.12±0.64
NG2	4.25±0.06	4.25±0.06	998.4±0.8	0.74	98.95±0.74
NG3	4.86±0.06	4.26±0.06	998.3±1.1	0.75	99.03±0.83
NX1	3.66±0.13	4.23±0.13	997.4±0.8	0.72	99.51±1.11
NX2	4.95±0.12	4.21±0.12	998.7±0.8	0.66	99.56±0.56
NX3	5.66±0.12	4.19±0.12	998.8±0.6	0.71	98.93±1.04
NS1	5.63±0.03	4.25±0.03	1002.3±1.2	0.45	100.23±1.08

NS2	6.13±0.09	4.23±0.09	1005.7±0.3	0.59	101.03±0.81
NS3	6.45±0.12	4.19±0.12	1003.8±0.6	0.53	100.6±0.72

3.2.6 *In-Vitro* drug release:

In-vitro drug release is the most important evaluation parameter of this study. As a sustained release formulations are meant to release the drug over a long period of time the in-vitro drug release profile must be evaluated. In this study, all the batches were evaluated for in-vitro drug release profile. Dissolution apparatus of paddle type (USP Type II) was used for the determination. Dissolution media used in the experiment was 900 ml, 0.1 N HCl for two hours and it was changed with 900 ml phosphate buffer ph 6.8 for further experiment. Temperature was adjusted at 37±0.5 ºc throughout the experiment. Paddles were rotated at 50 rpm. 5 ml samples were collected and 5 ml fresh media was added to the dissolution vessel at 1 hour interval for 12 hours. The samples were filtered with 0.45µ filter and diluted. Samples were analyzed using UV-Visible spectrophotometer at 232 nm wavelength. The %drug release was calculated and a graph of cumulative %drug release vs. time was plotted.

Preparation of standard curve

Standard curve for the dissolution study was obtained by preparing a series of solutions of metformin HCl. 100 mg metformin hydrochloride was weighed accurately and taken into a volumetric flask of 100ml, volume is made up by distilled water and solution was put in the sonicator for 30 minutes. 1 ml solution was pipette out and further diluted to 100 ml. prepared stock solution was diluted with distilled water as the quantity given in table 2. The absorbance of the resulting solutions was taken by UV-Visible spectrophotometer at 232 nm wavelength.

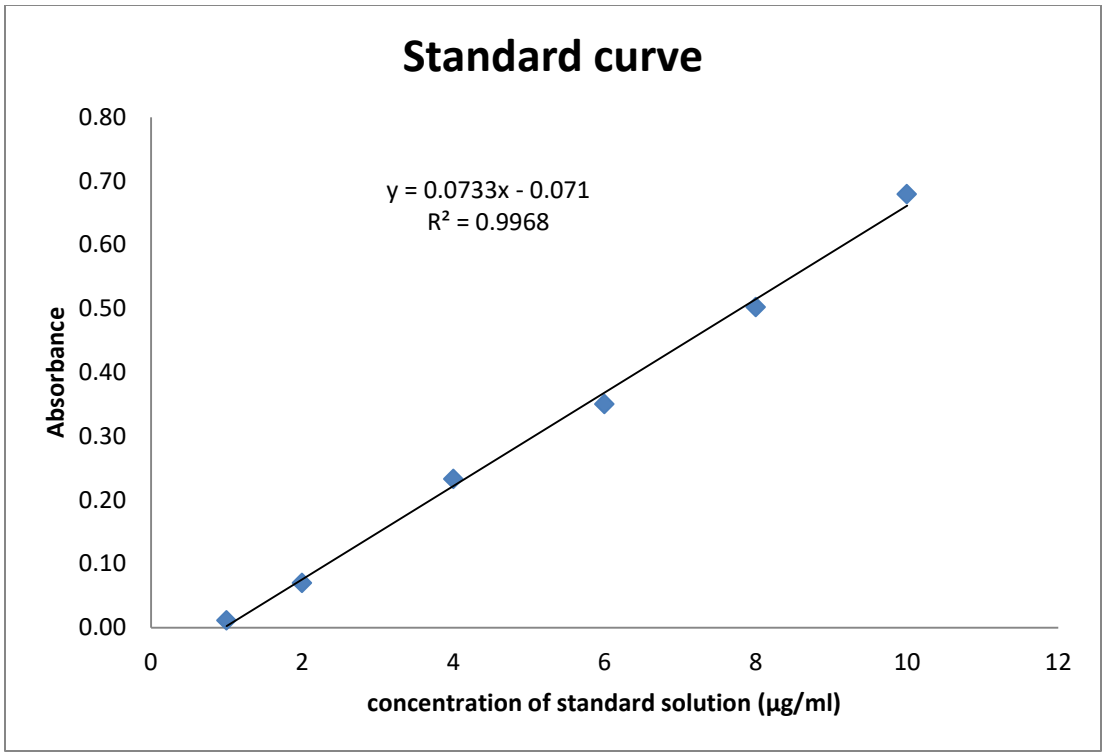
(Upadhyay et al., 2014)(Prabhu et al., 2008)(Chandrasekaran et al., 2011)

(Hu et al., 2006)(March & Tablets, 2010)

Sr. No.	Amount of stock solution(ml)	Amount of distilled water(ml)	Concentration (µg/ml)	Absorbance
1	1	9	1	0.011
2	2	8	2	0.070
3	4	6	4	0.233
4	6	4	6	0.350
5	8	2	8	0.502
6	10	0	10	0.679

[Table 5.Preparation of standard solution]

[Figure 1.Standard curve]



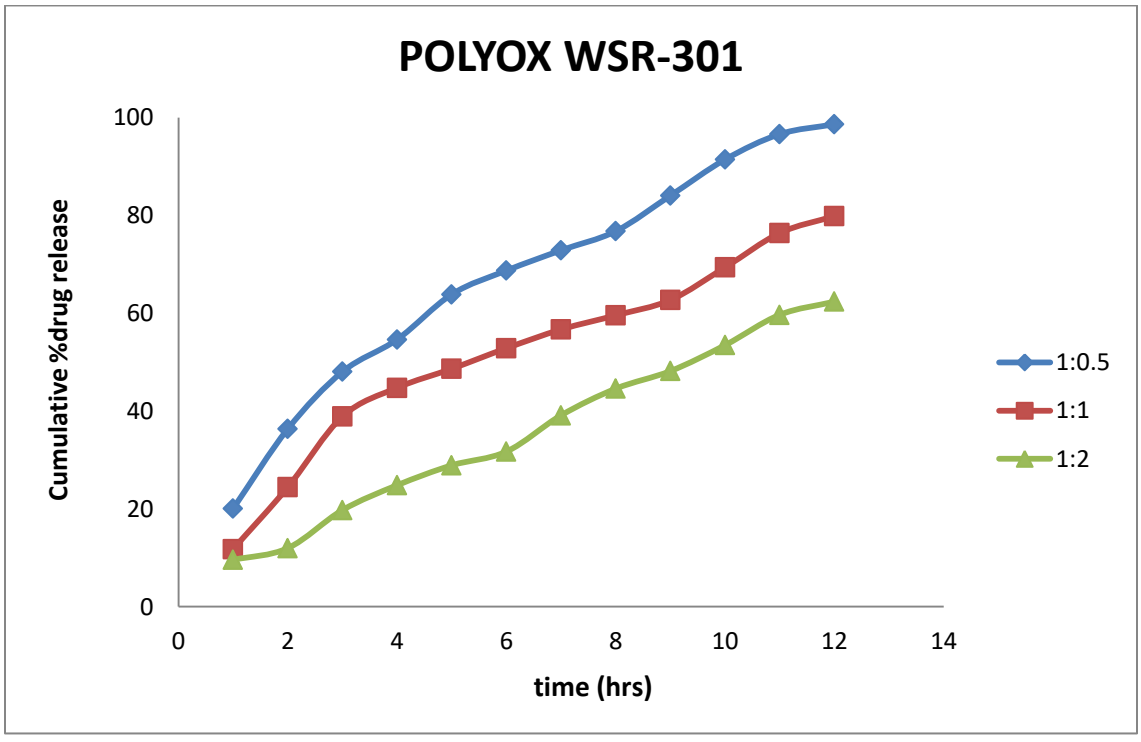
[Table 6.Cumulative %drug release]

TIME (hrs)	SP1	SP2	SP3	SE1	SE2	SE3	SH1	SH2	SH3
1	20.07	11.79	9.58	26.39	10.58	7.04	20.72	21.40	14.54
2	36.35	24.45	11.97	37.83	15.02	11.83	37.93	43.23	26.59
3	48.04	38.90	19.76	46.79	27.00	23.04	56.47	51.29	34.03
4	54.63	44.76	24.83	54.85	32.72	29.44	63.09	62.32	40.22
5	63.87	48.65	28.91	61.36	38.87	35.26	76.93	74.23	48.21
6	68.72	52.85	31.72	67.19	46.45	39.78	84.22	78.20	53.99
7	72.87	56.68	39.14	74.15	53.68	41.89	90.88	82.03	59.31
8	76.77	59.57	44.58	78.05	56.64	46.86	96.90	85.27	61.44
9	84.05	62.71	48.18	81.07	61.20	54.76	99.83	87.33	66.04
10	91.43	69.38	53.48	88.10	64.37	59.68	-	90.27	70.15
11	96.61	76.40	59.68	91.57	67.78	63.23	-	93.56	73.10
12	98.63	79.85	62.37	94.67	71.84	68.92	-	98.60	76.04

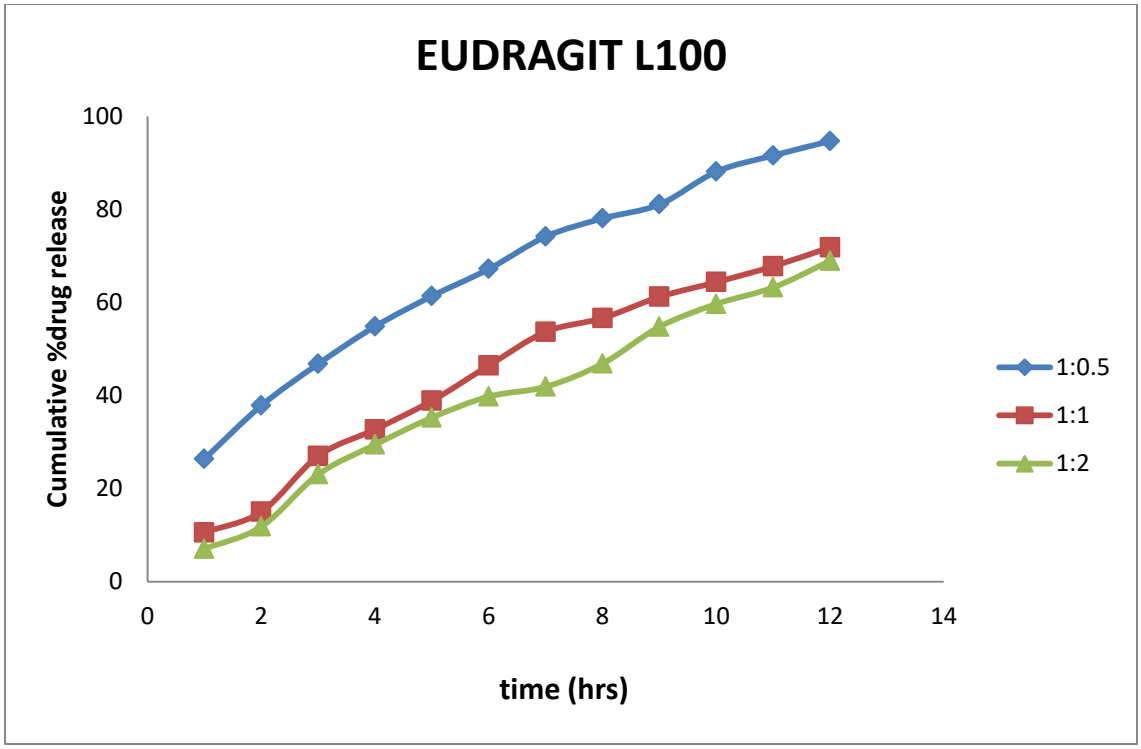
[Table 7.Cumulative %drug release]

TIME (hrs)	NG1	NG2	NG3	NX1	NX2	NX3	NS1	NS2	NS3
1	55.91	44.56	32.53	46.95	31.21	37.05	40.58	39.80	31.39
2	72.05	52.68	49.10	67.04	47.11	44.94	51.59	43.03	46.69
3	79.56	64.98	61.78	76.14	56.30	54.88	66.85	56.99	53.20
4	83.15	73.57	72.93	84.73	69.48	65.84	78.17	75.10	62.75
5	98.44	82.73	80.96	88.32	81.29	74.80	89.30	82.13	70.86
6	-	87.55	86.43	95.95	88.04	79.37	96.65	86.25	78.52
7	-	91.85	91.29	99.93	95.92	82.98	99.58	92.33	84.76
8	-	98.53	96.01	-	97.50	86.86	-	96.92	87.95
9	-	-	99.22	-	99.42	91.57	-	98.65	91.03
10	-	-	-	-	-	93.19	-	-	94.65
11	-	-	-	-	-	95.85	-	-	97.31
12	-	-	-	-	-	98.88	-	-	99.81

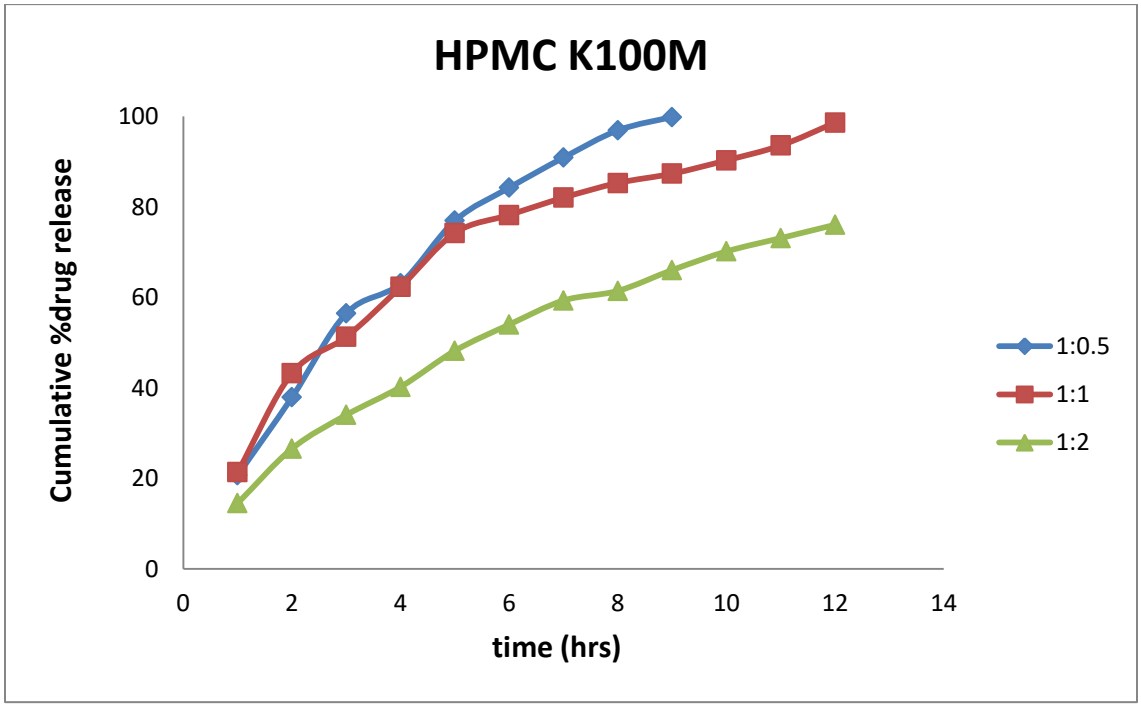
[Figure 2.Drug release curve for Polyox]



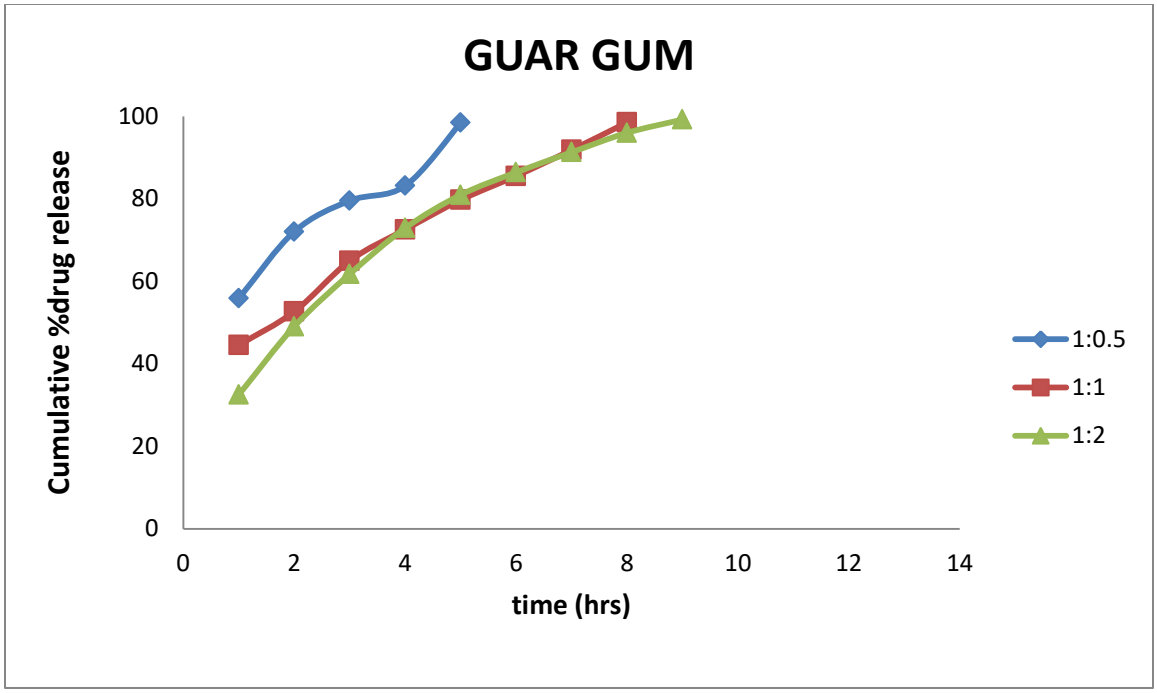
[Figure 3.Drug release curve for Eudragit]



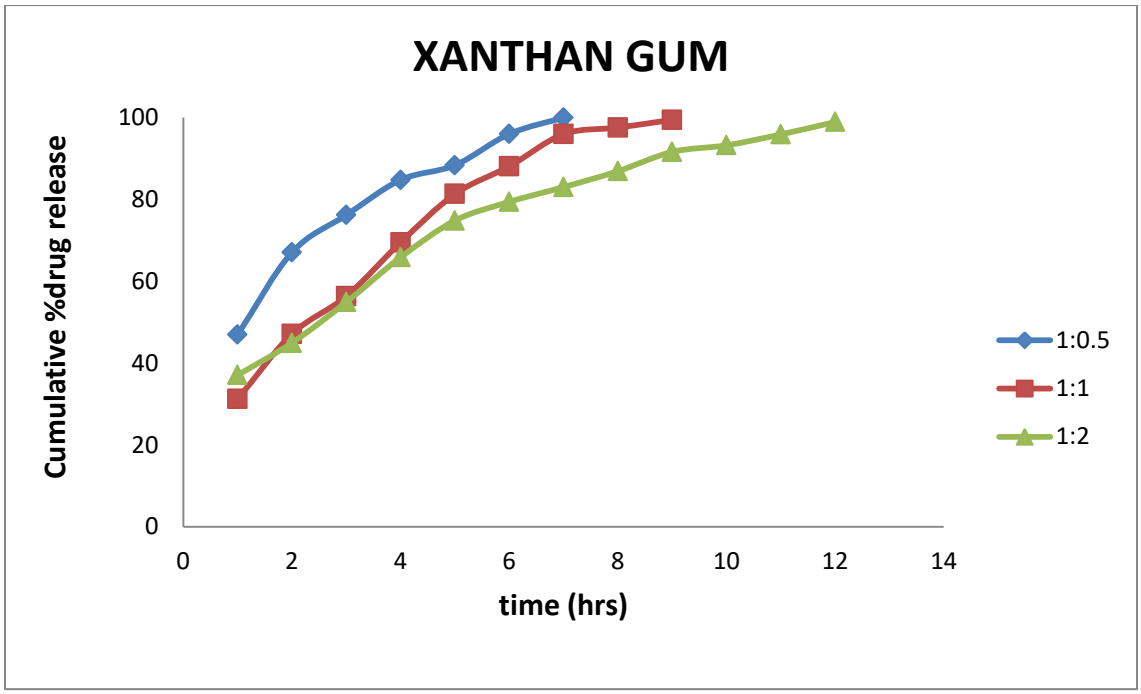
[Figure 4.Drug release curve for HPMC]



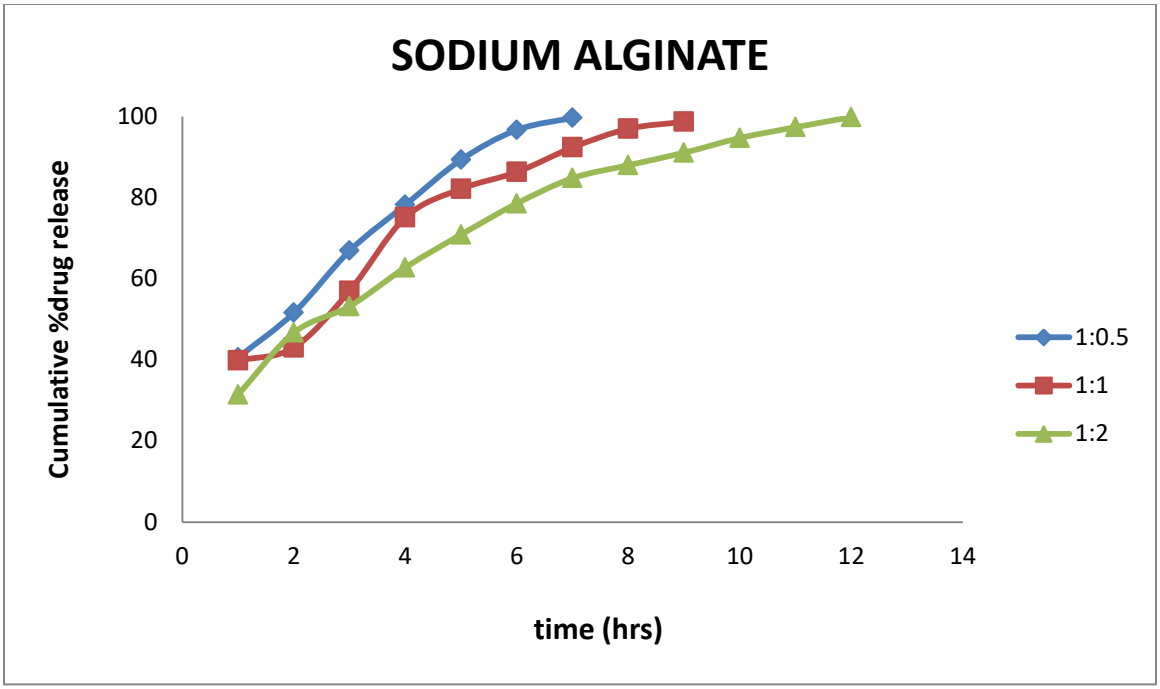
[Figure 5.Drug release curve for Guar gum]



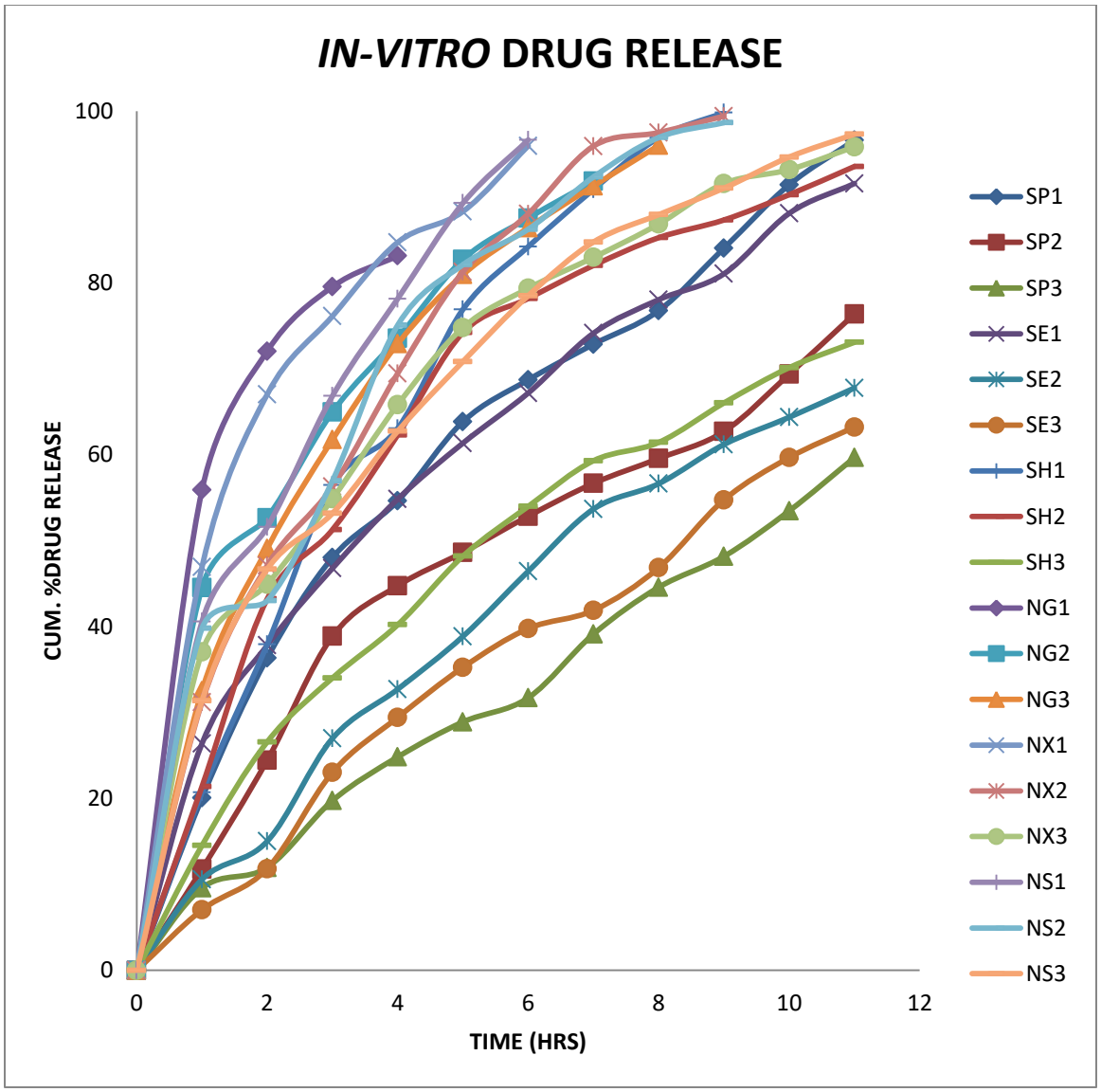
[Figure 6.Drug release curve of Xanthan gum]



[Figure 7. Drug release curve of Sodium alginate]



[Figure 8. Drug release curve of all 18 batches]



4. RESULT AND DISCUSSION:

In this study, different synthetic and natural polymers like Polyox WSR-301, HPMC K100M, Eudragit L100, Guar gum, Xanthan gum, sodium alginate were tested to impart release retardation for metformin HCl tablets. Synthetic and natural polymers were compared and results were obtained by various pre-compression and post-compression evaluation tests. Results of pre-compression and post-compression tests are given in table

3 and table 4 respectively. In-vitro drug release was checked and results were compiled in table 6 and table 7.

The results obtained from different evaluation parameters are arranged in the tables above. From the values of the table 3, angle of repose varies from 21.52±0.01 to 28.19±0.53 which shows good flow property of the powder blends. Similarly bulk density varies from 0.511 gm/cm^3 to 0.695 gm/cm^3 and tapped density varies from0.586 gm/cm^3 to 0.765 gm/cm^3. All the batches showed Carr's index between 6.142 and 16.993 and Hausner's ratio between 1.065 and 1.191.

In the table 4, the values of post-compression parameters are given. Hardness and thickness of the tablets ranges between 3.23±0.12kg/cm^2 to 6.95±0.06kg/cm^2 and 4.19±0.12mm to 4.26±0.06mm respectively. All the batches showed very less variation in weight and drug content. The average weight and drug content of tablets varies between 996±0.3mg to 1005±1.1mg and 98.45±0.71% to 101.63±0.96% respectively.%Friability was measured and values lies between 0.48% to 0.84% friability, which was within the limit of <1% friability. Small values for standard deviation showed less intra batch variations.

Dissolution test was performed for 12 hour's time period using USP type-II dissolution apparatus. The samples were taken at 1 hour interval and analyzed by UV-Visible spectrophotometer. Out of all 18 batches SP1, SE1, SH2, NX3 and NS3 showed desired drug release pattern as per USP. The standard values for dissolution test are given in table 8.

[Table 8. Standard values for dissolution test]

Time (hrs)	**Amount Dissolved (%)**
1	20-40
2	35-55
5	60-80
12	NLT 85

In this study, % drug release of batch SP1, SE1, SH2, NX3 and NS3 at 1 hr, 2 hr, 5 hr and 12 hr are given in table 9. Other batches from the experiment failed to comply the standard % drug release criteria as per USP.

[Table 9. Cumulative %drug release of selected batches]

Batch	**Cumulative %drug release**			
	1 hr	2 hr	5 hr	12 hr
SP1	20.07	36.35	63.87	98.63
SE1	26.39	37.83	61.36	94.67
SH2	21.40	43.23	74.23	98.60
NX3	37.05	44.94	74.80	98.60
NS3	31.39	46.69	70.86	99.81

5. CONCLUSION

In this experiment, an attempt was made to formulate sustained release tablets of metformin hydrochloride. For this purpose different synthetic and natural polymers were compared for their release retardation capacity. Different evaluation tests were performed and from the results, several conclusions were made. From the pre-compression tests it could be concluded that all the powder blends showed good flow properties. Results of post-compression tests led to the conclusion that all the tablet batches had optimum hardness and thickness. In addition to that, all tablet batches complied with weight variation test, friability test and content uniformity test.

Synthetic polymers showed desired release retardation at low concentration (Plyox WSR-301 and Eudrajit L100 at 1:0.5 and HPMC K100M at 1:1) while natural polymers at high concentration (Xanthan gum and sodium alginate at 1:2). On the other hand, Guar gum failed to impart desired release retardation.

6. REFERENCES:

1. Ashour, S., & Kabbani, R. (2003). Direct spectrophotometric determination of metformin hydrochloride in pure form and in drug formulations. *Analytical Letters*, *36*(2), 361–370. https://doi.org/10.1081/AL-120017696
2. Barzegar-Jalali, M., Hanaee, J., Omidi, Y., Ghanbarzadeh, S., Ziaee, S., Bairami-Atashgah, R., & Adibkia, K. (2013). Preparation and evaluation of sustained release calcium alginate beads and matrix tablets of acetazolamide. *Drug Research*, *63*(2), 60–64. https://doi.org/10.1055/s-0032-1331755
3. Chandrasekaran, A. R., Jia, C. Y., Theng, C. S., Muniandy, T., Muralidharan, S., & Dhanaraj, S. A. (2011). Invitro studies and evaluation of metformin marketed tablets-Malaysia. *Journal of Applied Pharmaceutical Science*, *1*(5), 214–217.
4. Corti, G., Cirri, M., Maestrelli, F., Mennini, N., & Mura, P. (2008). Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-β-cyclodextrin. *European Journal of Pharmaceutics and Biopharmaceutics*, *68*(2), 303–309. https://doi.org/10.1016/j.ejpb.2007.06.004
5. Dange, Y. D., Honmane, S. M., Bhinge, S. D., Salunkhe, V. R., & Jadge, D. R. (2017). Development and validation of uv-spectrophotometric method for estimation of metformin in bulk and tablet dosage form. *Indian Journal of Pharmaceutical Education and Research*, *51*(4), S754–S760. https://doi.org/10.5530/ijper.51.4s.109
6. Fukuda, M., Peppas, N. A., & McGinity, J. W. (2006). Properties of sustained release hot-melt extruded tablets containing chitosan and xanthan gum. *International Journal of Pharmaceutics*, *310*(1–2), 90–100. https://doi.org/10.1016/j.ijpharm.2005.11.042
7. Hu, L. D., Liu, Y., Tang, X., & Zhang, Q. (2006). Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets. *European Journal of Pharmaceutics and Biopharmaceutics*, *64*(2), 185–192. https://doi.org/10.1016/j.ejpb.2006.04.004
8. Khullar, P., Khar, R. K., & Agarwal, S. P. (1998). Evaluation of guar gum in the preparation of sustained-release matrix tablets. *Drug Development and Industrial*

Pharmacy, *24*(11), 1095–1099. https://doi.org/10.3109/03639049809089955

9. Košir, D., Ojsteršek, T., Baumgartner, S., & Vrečer, F. (2018). A study of critical functionality-related characteristics of HPMC for sustained-release tablets. *Pharmaceutical Development and Technology*, *23*(9), 865–873. https://doi.org/10.1080/10837450.2016.1264417
10. March, O., & Tablets, M. H. E. (2010). *Metformin Hydrochloride Extended-Release Tablets*. 1–7.
11. Nikam, V. (2011). Eudragit a versatile polymer : A review Pharmacologyonline 1 : 152-164 (2011) EUDRAGIT A VERSATILE POLYMER : A REVIEW. *Pharmacology Online*, *1*(January 2011), 152–164.
12. Prabhu, N. B., Marathe, A. S., Jain, S. K., Singh, P. P., Sawant, K., Rao, L., & Amin, P. D. (2008). Comparison of dissolution profiles for sustained release resinates of BCS class i drugs using USP apparatus 2 and 4: A technical note. *AAPS PharmSciTech*, *9*(3), 769–773. https://doi.org/10.1208/s12249-008-9110-4
13. Shah, K. R., Chaudhary, S. A., & Mehta, T. A. (2014). Polyox (Polyethylene Oxide) Multifunctional Polymer in Novel Drug Delivery System. *International Journal of Pharmaceutical Sciences and Drug Research*, *6*(2), 95–101. www.ijpsdr.com
14. Singh, S., Neelam, Arora, S., & Singla, Y. (2015). An overview of multifaceted significance of eudragit polymers in drug delivery systems. *Asian Journal of Pharmaceutical and Clinical Research*, *8*(5), 1–6.
15. Upadhyay, P., Nayak, K., Patel, K., Patel, J., Shah, S., & Deshpande, J. (2014). Formulation development, optimization, and evaluation of sustained release tablet of valacyclovir hydrochloride by combined approach of floating and swelling for better gastric retention. *Drug Delivery and Translational Research*, *4*(5–6), 452–464. https://doi.org/10.1007/s13346-014-0207-x
16. Wadher, K., Umekar, M., & Kakde, R. (2011). Study on sustained-release metformin hydrochloride from matrix tablet: Influence of hydrophilic polymers and in vitro evaluation. *International Journal of Pharmaceutical Investigation*, *1*(3), 157. https://doi.org/10.4103/2230-973x.85966

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