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Design and characterization of controlled release formulation of Mesna by using different polymers

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Abstract

The current study created a controlled-release formulation of Mesna to keep the drug at therapeutic levels for longer than ten hours. Eudragit L 100, Chitosan, HPMC K4M. The dose of mesna was set at 100 mg. The tablet's total weight was calculated to be 100 mg. Polymers were employed in concentrations of 50 mg, 100 mg, and 150 mg. Every formulation passed several physicochemical evaluation criteria and was determined to be within tolerances. However, it was clear from the dissolving trials that the formulation (F6) had a better and more desirable drug release pattern, achieving 96.47% in 10 hours. As a controlled release substance, it contains the naturally occurring polymer Mesna. The release kinetics mechanism was in zero order. The optimal formulation was used again for reproducibility, and conformance was tested in all quality control procedures. It was discovered that the outcomes were very impossible for one another. The optimized formula will be used for formulation development and other studies, such as bio-equivalency research, to ensure a successful product launch.

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INTRODUCTION

Most conventional oral drug preparations, including tablets and capsules, are designed to release the active ingredient as soon as the drug is taken orally to achieve quick and thorough systemic medication absorption. The beginning of concomitant pharmacodynamic effects and relatively quick drug absorption are the outcomes of such immediate-release medicines. Nevertheless, following the drug's pharmacokinetic profile, plasma drug concentrations decrease once drug absorption from the dose form is finished. Therapeutic action eventually wanes as plasma medication concentrations drop below the minimal effective plasma concentration (MEC). If a prolonged therapeutic impact is wanted, another dose is typically administered before reaching this point [1].

Using a dosage form that will offer sustained drug release and consequently maintain plasma drug concentrations beyond what is generally seen using immediate-release dosage forms is an alternative to providing another dose. The

conventional preferred drug administration method is oral intake, which offers a practical way to accomplish local and systemic effects efficiently. Minimal control over drug release exists in traditional oral drug delivery systems. Intermittently administering grossly large dosages can attain the effective concentration at the target site, but this usually leads to continuously fluctuating, unpredictable, and frequently sub or supratherapeutic plasma concentrations that have noticeable adverse effects. Oral controlled release drug delivery encompasses two types of delivery systems: those that deliver a drug continuously at predictable and reproducible kinetics for a predefined duration during GI transit and those that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action [2].

METHODOLOGY

Drug – Excipient compatibility studies

FTIR Spectroscopy:

We compared the physical characteristics of the physical mixture with those of a plain medication. After thoroughly combining the samples with 100 mg of potassium bromide IR powder, they were compressed for three minutes under vacuum at a pressure of around 12 psi. An appropriate holder was used to install the resulting disc in the Perkin Elmer IR spectrophotometer, and the IR spectrum was recorded between 3500 and 500 cm. Any changes in the spectrum were compared with the resulting spectrum [3].

Pre-formulation parameters [4][5][6]

After a tablet is formulated according to a guideline, the blend's physicochemical qualities often determine its quality. The qualities of the blends that are created can be influenced by a variety of formulations and process variables that are involved in mixing. The different attributes of mixtures were evaluated following Pharmacopoeia.

The angle of repose:

Calculating the frictional force in a loose powder can be done using the angle of repose. The most significant possible angle between the surface of the powder pile and the horizontal plane is defined as follows. To find the angle of repose, the following formula was utilized:

$$\tan \theta = h / r$$

Bulk Density:

The weight per unit volume is known as Density. Bulk Density is measured in grams per cubic centimeter and is determined by dividing the mass of the powder by the bulk volume. Using this formula, the bulk Density was calculated:

$$\text{Bulk Density} = M / V_o$$

Tapped Density:

The tapped volume, or V, was measured and rounded to the nearest graded unit after this process was repeated until the discrepancy between succeeding measurements was less than 2%. The following formula was used to get the tapped Density, in grams perL:

$$\text{Tap} = M / V$$

Measures of powder compressibility:

The Compressibility Index, called Carr's Index, determines how well a powder may be compressed. It is computed using the bulk and tapped densities. These changes are reflected in the Compressibility Index, calculated using the following formulas.

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Formulation development of Tablets:

Direct compression was used to make each formulation. Table 1 lists the components of the various formulations. The goal of the tablets, which were made following the instructions below, is to delay Mesna's release. The tablet's total weight was calculated to be 400 mg [7]. Each ingredient, including mesna, was separately run through a sieve with a no. of 60. Triturating for up to 15 minutes allowed all the components to be well combined. Talc was used to lubricate the powder combination. The direct compression method was used to prepare the tablets.

Evaluating post-compression parameters for delivered tablets

The physicochemical characteristics of the suggested formulation tablets, such as weight variation, hardness, thickness, friability, and drug content, were examined [8].

Table 1 Composition of the tablet formulation

INGREDIENTS in mg	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	110	110	110	110	110	110	110	110	110
HPMC K4 M	40	110	160	-	-	-	-	-	-
Chitosan	-	-	-	60	110	160	-	-	-
Eudragit L 100	-	-	-	-	-	-	60	110	160
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3
Microcrystalline cellulose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Weight variation test:

Twenty tablets were consumed, and the weight of each one was recorded separately and as a group on a digital scale to investigate the weight shift. We divided the total weight by the average weight of a tablet. The weight variation test would be an excellent approach to discourage drug content homogeneity mining effectively. The following table indicates the percentage deviation of each weight from the average weight. Only two weights depart beyond this limit, and none exceed this limit by more than double [9]. Determined were the mean and deviation. Using the following formula, the % deviation was determined.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness:

The hardness of a tablet is defined as the force needed to break it throughout its diameter. When handled and kept before use, the tablet's resistance to abrasion, chipping, and breaking depends on its hardness. Using a Monsanto hardness tester, three tablets were tested for hardness for each formulation; the average result was computed and provided with a deviation [10].

Thickness:

The thickness of the tablet plays a significant role in appearance reproduction. The average thickness is computed and shown with a deviation for both coated and core tablets [11].

Friability:

It gauges the tablets' mechanical strength. The process was followed to determine the friability using the Roche friability. The friability held pre-weighed tablets. The tablets were spun for four minutes at 25 rpm or 100 revolutions [12]. When the tablets were reweighed after the test, the weight loss represents the degree of friability and is given as a percentage.

% Friability = [(W1-W2) / W] × 100

Drug content determination:

Drug content in tablets was tested. Ten finely powdered tablets—equivalent to one tablet weight of Mesna—were carefully weighed, placed in a 100 ml volumetric flask with 50 ml of water, and left to stand to ensure total drug solubility. Water was added till the mixture reached its total volume. After properly diluting the solution, a UV-visible spectrophotometer was used to measure the absorption [13]. The calibration curve served as the basis for calculating the drug's concentration.

***In vitro* drug release studies**

After filling the jar with 900 ml of 0.1 HCl, the USP apparatus II (Paddle Method) was put together. The medium was left to reach an equilibrium temperature of 37°C +/- 0.5°C. After inserting the tablet and covering the vessel, the apparatus was run for two hours. After that, the medium containing 0.1 N HCl was withdrawn, and pH 6.8 phosphate buffer was added. The operation was then carried out for twelve hours at 50 rpm. Five milliliters of the receptor fluid were removed, filtered, and added back after a predetermined time [14]. Receptor fluid was diluted appropriately, and using a UV spectrophotometer, the samples were measured spectrophotometrically at 238 nm.

The use of Release Rate Kinetics for Dissolution Data:

Several models were employed to examine the drug release kinetics. The collected data were fitted into zero-order, first-order, Higuchi, and Korsmeyer-Peppas release models to investigate

the mechanism underlying the dosage form's drug release rate kinetics [15]-[18].

Zero-order release rate kinetics:

The release rate data were fitted to the subsequent equation to examine the zero-order release kinetics.

$F = K_o t$

First-order release rate kinetics: The following equation fits the release rate data.

$Log (100-F) = kt$

Higuchi release model: To examine the Higuchi release kinetics, the release rate data were fitted to the subsequent equation.

$F = k t1/2$

Korsmeyer and Peppas release model:

Plotting the log proportion of drug released versus log time using the Korsmeyer-Peppas equation allowed for evaluating the drug release mechanism. The drug release mechanism, as determined by the slope of the straight line, is shown by the exponent "n."

$M_t / M_\infty = K t^n$

Hixson-Crowell release model:

The Hixson-Crowell model uses erosion to explain how pharmaceuticals are released from insoluble matrices. (Where the diameter and surface area of the tablets or particles fluctuate).

$(100-Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$

RESULTS AND DISCUSSION

Drug and excipient compatibility studies:

FTIR Studies

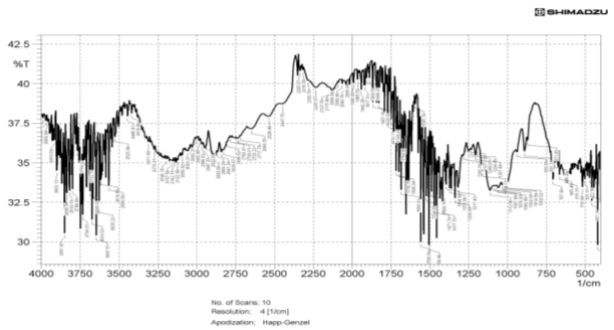

Figure 1 FTIR Spectra of Pure Drug

Table 2 Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.12	0.48±0.05	0.55±0.05	15.22±0.07	0.87±0.07
F2	25.68	0.51±0.08	0.53±0.05	15.88±0.06	0.99±0.06
F3	25.55	0.52±0.06	0.57±0.06	16.12±0.02	0.65±0.04
F4	25.44	0.52±0.07	0.55±0.08	16.68±0.09	1.13±0.05
F5	25.35	0.53±0.04	0.58±0.04	17.93±0.05	1.25±0.09
F6	24.23	0.52±0.05	0.57±0.07	16.66±0.08	1.07±0.08
F7	25.19	0.53±0.07	0.58±0.05	17.44±0.06	0.77±0.04
F8	24.23	0.57±0.05	0.68±0.03	16.98±0.03	1.16±0.08
F9	25.06	0.56±0.09	0.52±0.04	17.54±0.08	1.17±0.03

Table 3 Tablet quality parameters for in-vitro evaluation

Formulation	Weight variation (mg)	Hardness (kg/cm2)	Friability (% loss)	Thickness (mm)	Drug content (%)
F1	102.5	4.4	0.51	1.7	98.77
F2	105.4	4.4	0.52	1.8	98.46
F3	98.6	4.3	0.52	1.8	98.35
F4	101.6	4.4	0.56	1.8	99.88
F5	109.4	4.3	0.57	1.6	99.15
F6	99.7	4.4	0.46	1.6	98.57
F7	98.3	4.2	0.52	1.3	98.43
F8	101.2	4.2	0.48	1.6	99.66
F9	98.3	4.4	0.56	1.5	99.13

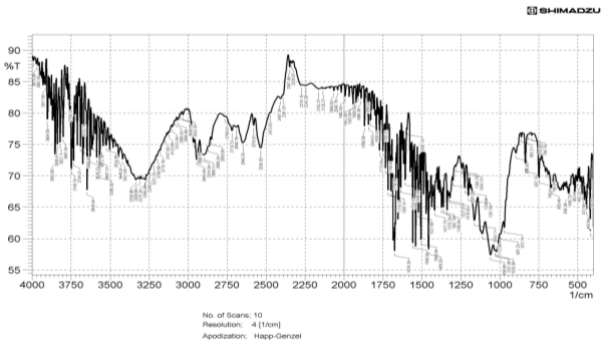

Figure 2 FTIR Spectra of optimized formulation

Pre-formulation parameters:

A combination of tablet powder was pre-formulated according to different specifications. The powder blend exhibits good flow qualities, as indicated by the values of the angle of repose. All the formulations' bulk densities were found to vary from 0.49 to 0.58 (gm/cm3). All the formulations' compressibility indices ranged from 16 to 18, indicating that the powder had good flow characteristics. The powder has good flow qualities, as indicated by all formulations with Hausner ratios between 0 and 1.2.

Quality Control Parameters For tablets:

Quality control testing for tablets was conducted on the compression-coated tablet, including weight variation, hardness and friability, thickness, and drug release experiments in various media.

It was discovered that every metric, including weight fluctuation, friability, hardness, thickness, and drug content, was within acceptable bounds.

***In-Vitro* Drug Release Studies**

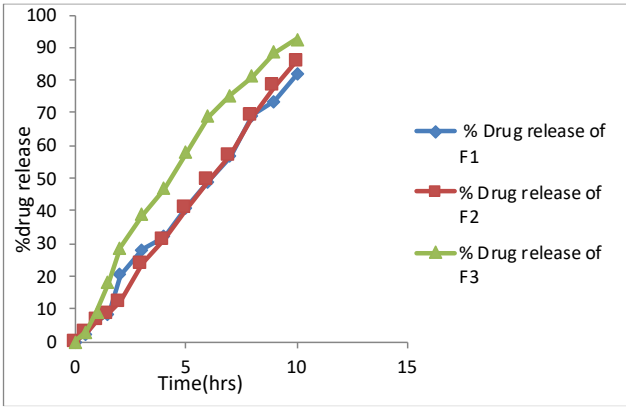

Figure 3 Formulation F1, F2, F3 dissolution graphs

Table 4 Mesna Tablets' cumulative percentage of drug release

Time (hrs)	% Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	2.34	2.68	2.89	2.59	12.5	12.87	13.36	3.25	5.10
1	7.04	6.18	9.09	7.65	15.34	16.77	17.24	11.87	10.54
1.5	8.01	8.59	17.98	15.27	20.54	22.09	19.79	20.16	19.75
2	20.31	12.00	28.87	12.73	45.78	33.03	25.00	28.61	27.19
3	28.15	23.96	38.77	20.30	57.55	47.15	27.51	35.81	31.97
4	32.17	31.27	46.78	32.57	61.60	55.38	33.14	40.83	42.45
5	41.07	40.79	57.77	40.03	67.63	60.19	42.50	51.62	50.13
6	49.03	49.33	68.98	55.62	70.20	73.38	52.56	61.04	59.14
7	56.50	56.92	75.43	61.35	75.76	80.27	60.05	70.12	64.93
8	69.15	69.06	81.34	72.53	81.60	87.44	74.92	77.54	70.54
9	73.39	78.12	88.67	84.87	86.82	93.24	83.88	81.67	75.19
10	81.78	85.67	92.67	89.03	90.92	97.47	91.59	90.56	87.51

Table 5 Tablet quality parameters for in-vitro evaluation

Code	Zero-order		First order		Higuchi		Peppas		Best fit model
	R^2	K_0 mg/h^{-1}	R^2	K_1 (h^{-1})	R^2	K (mg $h^{-1/2}$)	R^2	N	
F6	0.9724	4.6413	0.9471	2.0504	0.8364	13.945	0.9798	1.4375	Zero-order

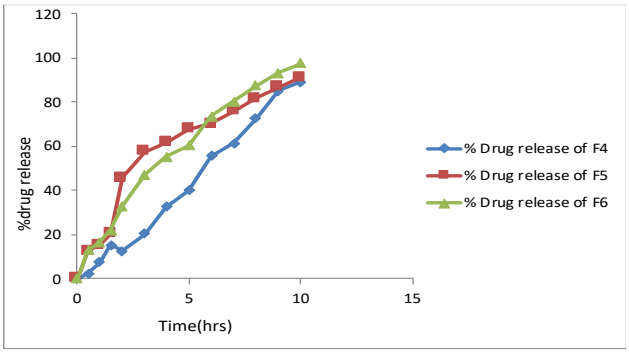

Figure 4 Formulation F4, F5, F6 dissolution graphs

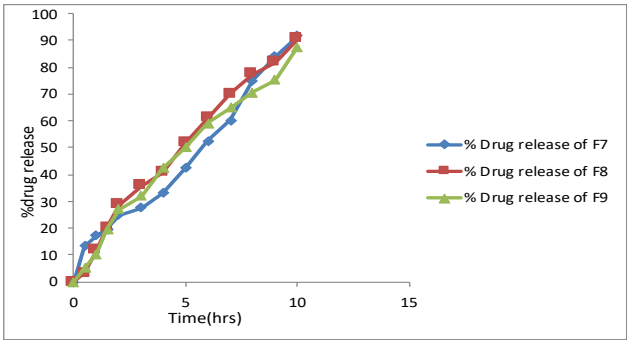

Figure 5 Formulation F7, F8, F9 dissolution graphs

It was clear from the dissolving results that the formulations made with chitosan as the polymer and HPMC K 4M could not delay the drug release for ten hours.

On the other hand, the formulations made with chitosan delayed the release of the drug at a dose of 150 mg (F6 Formulation). These formulations demonstrated the required release pattern, which included a maximum delay of 97.47% in 12 hours and a retardation of up to 10 hours.

Application of Release Rate Kinetics to Dissolution Data:

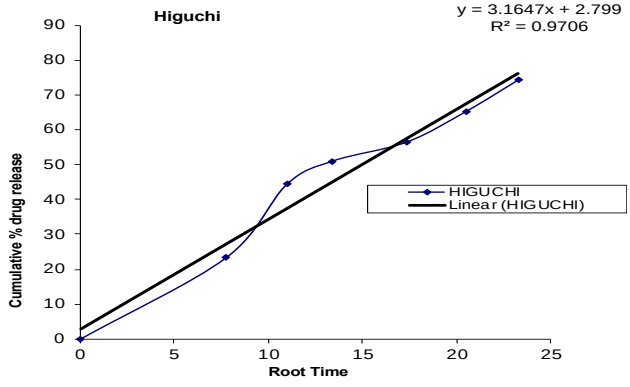

Figure 6 Kinetic model-Higuchi

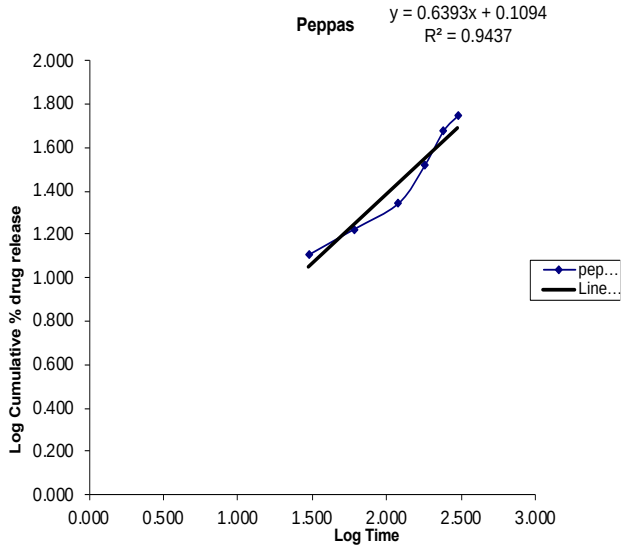

Figure 7 Kinetic model-Peppas

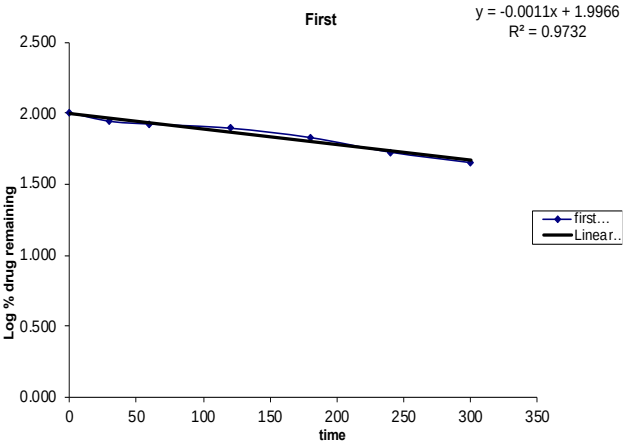

Figure 8 Kinetic model First order

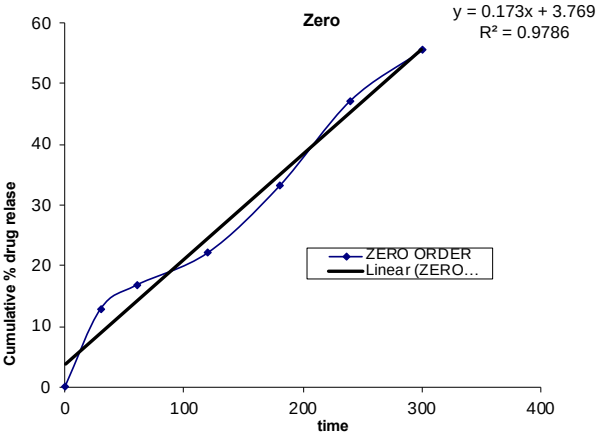

Figure 9 Kinetic model Zero order

CONCLUSION:

The current study created a controlled-release formulation of Mesna to keep the drug at therapeutic levels for longer than ten hours. Eudragit L 100, Chitosan, HPMC K4M. The dose of mesna was set at 100 mg. The tablet's total weight was calculated to be 400 mg. Polymers were employed in concentrations of 50 mg, 100 mg, and 150 mg. Every formulation passed several physicochemical evaluation criteria and was determined to be within tolerances. However, it was clear from the dissolving trials that the formulation (F6) had a better and more desirable drug release pattern, achieving 96.47% in 10 hours. As a controlled release substance, it contains the naturally occurring polymer Mesna. The release kinetics mechanism was in zero order. The optimal formulation was used once more for reproducibility, and conformance was tested in all quality control procedures. It was discovered that the outcomes were very impossible for one another. The optimized formula will be used for formulation development and other studies, such as bio-equivalency research, to ensure a successful product launch.

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REFERENCES

[1] K.Urukundu1 and N.Srinivas1 Formulation And Evaluation Of Sustained Release Matrix Tablets Of Zidovudine International Journal of Pharmaceutical Research & Analysis / Vol 5 / Issue 2 / 2015 /58-70

[2] Neha M Dembla1, Arun Pandian Maniyam2 and Surendra Agarwal3 Formulation Development and Evaluation of Gabapentin Controlled Release Tablets Pharm Pharmacol Int J 2015, 2(3): 00021

[3] R. Asija, S. Asija, S. Bhatt, A. Gupta, A. Shah, and P. Sharma Design And Development Of Controlled Release Tablet Of Losartan Potassium ARPB, 2015; Vol 5 (I)

[4] Patel Mubarak Husen, P Ashok Kumar, Suresh V Kulkarni, Someshwara Rao B Design And Evaluation Of Controlled Release Matrix Tablets Of Metoclopramide Hydrochloride Using Hydrophilic Polymers *I*nternational Journal of Current Pharmaceutical Research ISSN- 0975-7066 Vol 4, Issue 3, 2012

[5] Sayed AR, Gamal MM, Badry M. Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets. Saudi Pharm J 2009; 17:283-8.

[6] Carnali J O, Naser M S. The use of dilute solution viscosity to characterize the network properties of carbopol microgels. Colloid & Polymer Sci 1992; 270(2): 183-93.

[7] Garcia Gonzalez N, Kellaway I W, Fuente H, Anguiano, I S, Charro B Otero, Espinar F J et al. Influence of glycerol concentration and carbopol molecular weight on swelling and drug release characteristics of metoclopramide hydrogels. Int J Pharm 1994; 104:107-13.

[8] T. P. Hadjiioannou, G. D. Christian, M. A. koupparis. Quantitative calculations in pharmaceutical practices and research New Dehli, NY- VCH publishers Inc, 1993, pp. 345- 348. Edn, vol.3, Marceel Dekker, 1990, pp. 199-302.

[9] D. W. Bourne. Pharmacokinetics. In: G. S. Banker, C. T. Rhodes, eds. Modern Pharmaceutical, 4th ed. New York, NY, Marcel Dekker Inc, 2002, pp.67-92.

[10] T. Higuchi. Mechanism of sustained action medication, Theoretical analysis of release rate of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52:1145-1149(1963).

[11] Korsmeyer R W, Gurny R, Doelker E, P. Buri, and N. A. Peppas. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm. 1983; 15: 25-35.

[12] Emeje M, Olaleye O, Isimi C, Fortunak J, Byrn S, Kunle O, Ofoefule S. Oral Sustained Release Tablets of Zidovudine Using Binary Blends of Natural and Synthetic Polymers. Biol. Pharm. Bull, 33(9), 2010, 1561-1567.

[13] Mohd AH, Rao SA, Martha S, Sirisha Y, Chandrika PU, Development of a floating

multiple unit controlled release beads of zidovudine for treating AIDS. J. of Pharm. Res, 6, 2013, 78-83.

[14] Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. J. of Cont. Rel, 154, 2011, 2–19.

[15] Pawan P, Mayur P, Ashwin S. Role of natural polymers in sustained release drug delivery system: applications and recent approaches. Int. Res. J. Pharm, 2 (9), 2011, 6-11.

[16] Ansel HC, Loyyd VA., 1999 "Pharmaceutical dosage forms and drug delivery system." Lippincott's Williams and Wilking, Hong Kong. 8:275-80.

[17] Bonferoni MC, Rosi ST. 1993. "On the employment of λ-carrageenan in a matrix system. I. Sensitivity to dissolution medium and comparison with Na carboxymethylcellulose and xanthan gum." J.control Rel. 26:119.

[18] Sujja AJ, Munday DL, Khan KA. 1999 "Development and evaluation of a multiple-unit oral sustained release dosage form for S (+)-ibuprofen: preparation and release kinetics." Int. J.Pharm.193:73-84.