Study of Drug Release Kinetics from Sustained Release Matrix Tablets of Acyclovir using Natural Polymer Obtained from *Colocasia Esculenta*

Dharmendra Solanki[1*], Mohit Motiwale[2], Sujata Mahapatra[3]

[1]College of Pharmacy, Shri Ram Murti Smarak College of Engineering and Technology (SRMS CET), Bareilly (UP) 243202, India
[2] Faculty of Pharmacy, VNS Group of Institutions, Bhopal (MP), India
[3] Department of Botany, Ramadevi Women's University, Bhubaneswar (Odisha) , India

Abstract : Sustained-release (SR) matrix tablets of Acyclovir and polysaccharide isolated from corms of *Colocasia esculenta,* at different drug to polymer ratios, were prepared by using wet granulation method. The formulated tablets were also characterized by physical and chemical parameters and results were found in acceptable limits. The investigation focuses on the influence of the proportion of the matrix material on the mechanism and the release rate of the drug from the tablets. In vitro drug release appears to occur both by diffusion and a swelling-controlled mechanism, indicates the drug release from the tablet was non-Fickian super case II transport. The drug release data fit well to the Zero-order drug release Model and the Korsmeyer equation.
Keywords : Acyclovir, Sustained-release, *Colocasia esculenta*, Natural polysaccharide, *etc*.

Introduction:

Sustained Release provides the most desirable dosing regimens with effective pharmacokinetic profile and pharmacodynamic response in chronic therapy. This approach prevents the patient from experiencing pain intermittently through maintenance of consistent drug input and it may alleviate the variability involved in the administration of multiple doses per day[1]. Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form, ease of scale-up and process validation. The

primary goal of matrix controlled drug delivery system is to sustained drug release in the body to enhance the drug absorption process in a specific manner and to facilitate intimate contact of the dosage form with underlying absorption surface to improve and enhance the bioavailability of drugs. The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it's release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant supports to disintegration. Hydrophillic polymer matrix systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Drug release from hydrophillic matrix is known to be a complex interaction between dissolution, diffusion and erosion mechanisms [2].

Natural polymer plays a significant role in the formulation development of new controlled release dosage forms as well as in human health care system. In recent years, natural polymer are growing rapidly and it continues to remain and important in the new formulation development of the controlled release dosage form. Natural polymers are much safer than synthetic. They provide many applications in the formulation development of a new controlled release dosage form, such as binder, disintegrator, diluents and release modifier. Acyclovir is an antiviral drug, it is given in conventional dosage form five times a day hence frequent administration is the major problem associated with it[3]. Therefore present study is aimed investigate the modified release characteristic of Acyclovir using natural polymer.

Material & Methods:

Fresh *Colocasia Esculenta* corms were bought from local market for the extraction of the polysaccharide. Acyclovir was received as a gift sample from Quimica Sintetica , S. A., Mumbai. Lactose monohydrate, Magnesium stearate and Talc purchased from Sunchem and Lobachemie pvt.Ltd. Mumbai, all other chemical reagents used were of analytical grade.

Isolation of Polymer material from *Colocasia esculenta* [4-6] :

About 200 gm of Fresh taro corms were washed to polish off the adherent soil material later peeled and Soaked in water for 12 hour and made in a smooth paste. Taro corm paste was suspended in 1% NaCl solution and stood for 1 hour. The slurry was passed through a muslin cloth. The filtrate was collected and an equal amount of acetone was added and stirred for few minutes, the mucilage was carefully separated. The mass then dried in a tray drier until it completely dried. After complete drying the powder was sieved using mesh #20 and stored for further use. It was characterize for yield, appearance, pH, viscosity flow properties etc[6-8].

Formulation of Sustained Release Matrix Tablet of Acyclovir [9-10]:

Different tablet formulations were prepared by wet granulation method by the given formula in table no. 1. All the powders were passed through mesh 60# sieve. Required quantity of drug and natural polymer were mixed and a sufficient quantity of granulating agent was added slowly. After enough cohesiveness was obtained the mass was sieved through 22/44 # mesh. The granules were dried at 40ºC for 12 hr. and added magnesium stearate as lubricant. The practical weight of tablet was calculated based on the drug content and polymer ratio of the granulation, and the tablets were compressed using a single punch tablet compression machine.

Table No. 1: Formulation formulas for matrix tablet

S.no	Ingredients	F1	F2	F3	F4	F5	F6
1.	Drug	200	200	200	200	200	200
2.	Lactose	265	240	215	190	165	140
3.	Polymer (taro gum)	50	100	125	150	175	200
4.	Talc	5	5	5	5	5	5
5.	Magnesium stearate	5	5	5	5	5	5

Each quantity was mentioned in mg, and total weight of the tablet = 500 mg

Tablet Evaluation [10-13]**:** Tablets were subjected to various precompression and post compression physical tests which include flow properties, weight variation, thickness, hardness, friability as per IP official methods.

Drug content uniformity: -Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1N HCl, the drug content was determined measuring the absorbance at 255 nm after suitable dilution using a UV- Vis double beam spectrophotometer Shimadzu 1800, Japan.

Compatibility study:- FTIR spectroscopy was performed on Fourier transformed infrared spectroscopy. The pellets of the acyclovir and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr press and the spectra were scanned in the wave number range of 4000-600 cm-1.

Swelling studies: - The extent of swelling was measured in terms of percentage weight gain by the tablet. Five tablets were accurately weighted and placed in the basket of USP dissolution apparatus, rotating at 50 rpm and 0.1N HCl was used as medium. The temperature was maintained at 37 ± 0.5^0C at the end of 4 h, the tablet were withdrawn, soaked with tissue paper and weighted. The percent increase in weight due to absorbed liquid or water uptake was estimated at each time point.

***In-vitro* drug release testing: -** The *in-vitro* release of Acyclovir from the formulated tablets was carried out in Tablet dissolution tester USP- Electro lab USP- TDT- 08L using 900 ml of dissolution medium maintained at 37.0 ±0.5°C and a stirring rate of 100 rpm. Six tablets from each formulation were tested individually in simulated gastric fluid (pH 1.2) for the first 2 h and in phosphate buffer (pH 6.8) for the following 10 h. At every 1 h interval, samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the amount of DS resent in each sample was determined Spectrophotometrically at 255 nm.

Data Analysis: To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration [14]. The first order Eq. (2) describes the release from system where release rate is concentration dependent [15]. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3) [16].

$$C = k_o t \qquad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_o - kt/2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$Q = Kt1/2 \qquad (3)$$

Where, K is the constant reflecting the design variables of the system.

Korsmeyer *et al* derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model [17-19]:

$$Mt / M\infty = Kt^n \qquad (4)$$

Where Mt / M∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent, which characterize the drug transport mechanism. When n=0.45, the drug diffuses through and is release from the polymeric matrix with a Fickian diffusion mechanism. For 0.45 < n < 0.89 an anomalous, non-Fickian diffusion occurs. When n= 0.89, Case II could be observed. For n<0.89 Super Case II diffusion occurs.

The following plots were made: *cumulative % drug release vs. time* (Zero order kinetic model); *log cumulative of % drug remaining vs. time* (First order kinetic model); cumulative *% drug release vs. square root of time* (Higuchi model) *log cumulative % drug release vs. log time* (Korsmeyer model)

Results and Discussion:

Characterization of mucilage: The polysaccharide obtained after extraction white in colour (colocasia esculenta). The viscosity was found to be 1.1152 cps. The pH was found to be 6.5.

Taro gum was isolated from Colocasia esculenta (Corms) and characterized. Percent yield was calculated 21%. Bulk density of taro gum was found to be 0.66g/ml and tapped density was found to be 0.8 g/ml. swelling index of the taro gum was 27 %. carrs index and hausners ratio was respectively found to be 25% and 1.212. Angle of repose of taro gum was found to be 25^0.

Pre-compression characterization: The flow properties for the formulated blend was carried out and the results were shown in table 2 It concludes all the formulations blend, angle of repose was found to be in the range from 20-25 its indicate well to passable flow of granules. Compressibility index was found in the range from 13.04 % -28.57 % indicating the powder blend has the excellent to good flow property for compression.

Post-compression characterization: Microscopic examinations of all the tablets formulations were found to be circular shape with no cracks. The measured hardness of tablets of each batch ranged between 5.33 to 7.66 kg/cm^2 (Table 2). This ensures good handling characteristics of all batches. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

The percentage weight variations for all formulations were tabulated in Table 2**.** All the formulated tablets passed weight variation test as the Avg. weight variation was within the Pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Drug Content (%) -The drug content for all the formulated tablets was found to 97.76% to 99.18 % of Acyclovir (Table 2). It complies with official specifications.

Table No. 2: Pre & Post Compression Characterization of Acyclovir Matrix Tablet

| Batch No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Housner Ratio	Angle of Repose (°)	Weight Variation (Av. Wt) (n=20)	Hardness kg/cm2 (n=3)	Friability (%) (n=20)	Drug Content (%) (n=3)
F-1	0.51	0.66	22	1.29	25	0.499	7.66	0.86	99.18
F-2	0.5	0.706	28.57	1.41	24	0.488	5.33	0.97	98.65
F-3	0.66	0.759	13.04	1.15	20	0.492	6.33	0.78	99
F-4	0.66	0.779	15.27	1.18	22	0.496	7.66	0.65	98.20
F-5	0.625	0.781	19.97	1.25	21	0.498	6.66	0.36	97.76
F-6	0.571	0.751	23.96	1.31	24	0.488	7.33	0.56	98.11

where n is number of Tablets.

Drug - excipient compatibility study: Compatibility study of drug and Polysaccharide was conducted by employing I.R. Spectral studies. The IR spectrum of Acyclovir, Taro gum and their physical mixtures are shown in Figure The following characteristic peaks were observed with Acyclovir C=N- (stretching) 1699.34 cm-1, C-N- (stretching) 1535.39 cm-1, N-H- (stretching) 3446.91 cm-1. As the identical principle peaks were observed in all the cases. Hence it shall be confirmed that interactions do not exist between the drug and polymer.

(A)   **(B)**

(C)
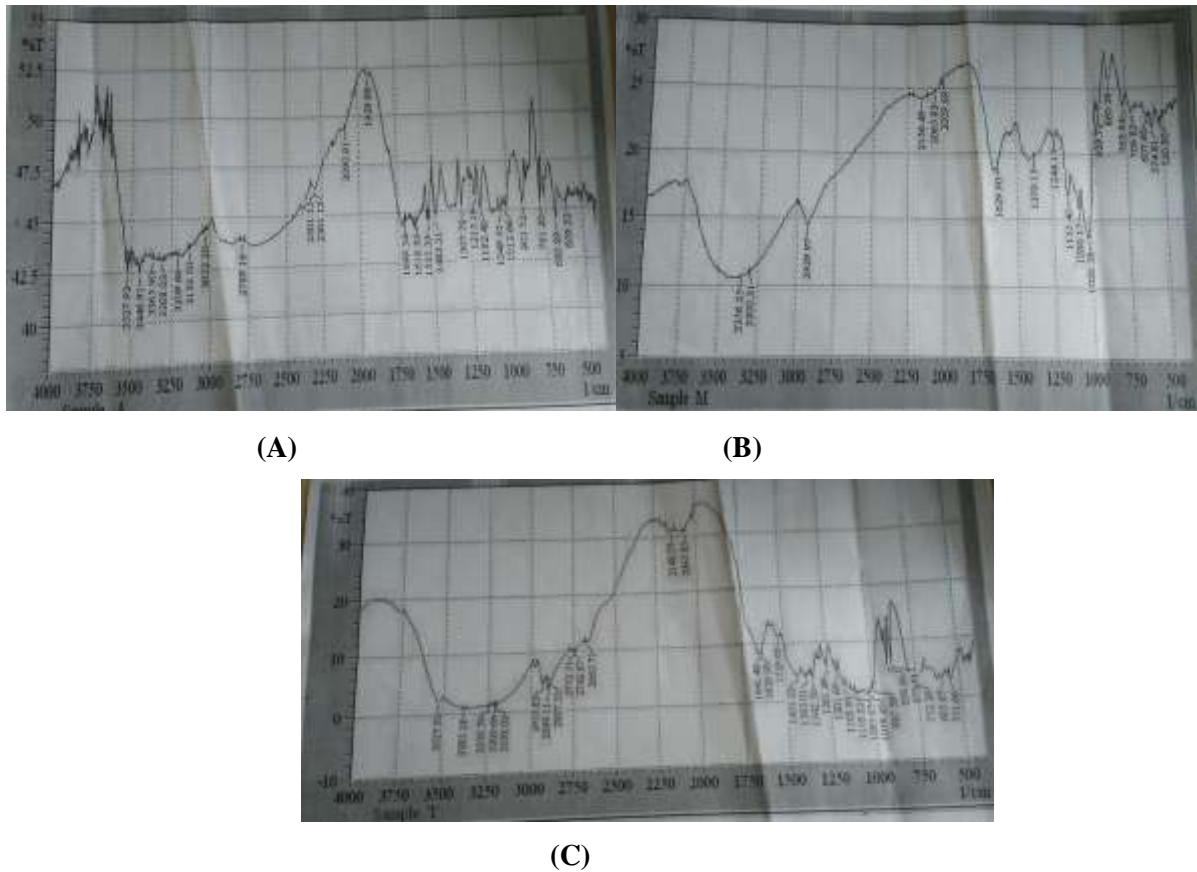
Fig.1: FTIR spectra showing (A) Acyclovir (B) Taro polysaccharides (C) Physical mixture of drug and excipients.

Swelling Studies:- The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulation F1 to F6 was studied 61.8% - 77.8 % (Fig.2).
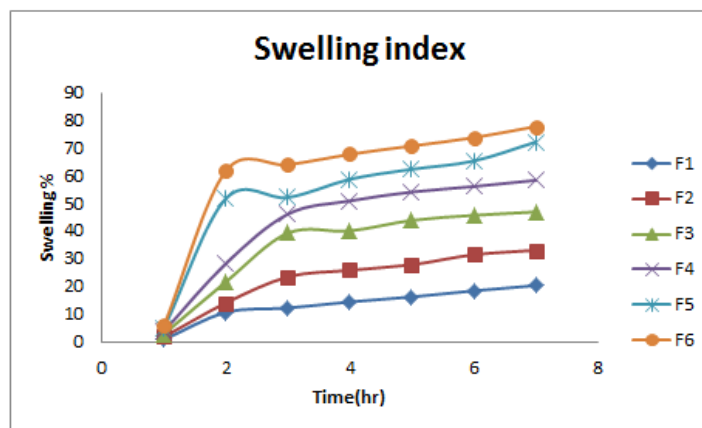
Fig. 2: Swelling behavior of Sustained Release-matrix tablets of Acyclovir.

***In-vitro* drug release study:** *In vitro* drug release profile of the prepared Acyclovir Matrix tablets was studied. The release data obtained from all the formulations shown in fig.3. The release of drug from the Tablet exhibited a sustained & controlled pattern over an extended time period. The formulation F1 containing 0.5% of polymer released 97.40% of drug after 12 hr. The formulation F2 containing 1% of polymer released 95.51% of drug after 12 hr. The formulation F3 containing 1.25% of polymer released 90.10% of drug after 12 hr. The formulation F4 containing 1.50% of polymer released 88.21% of drug after 12 hr. The formulation F5

containing 1.75% of polymer released 87.94 % of drug after 12 hr. The formulation F6 containing 2% of polymer released 85.33% of drug after 12 hr. this data indicating that as polymer increased drug release decreased. It may be due to swelling property of gum, as tablet swelled diffusion path length increases. Lactose particles might contribute to the increased compressibility and produce more uniform matrices with uniform channels for water to diffuse and to dissolve the drug in a sustained release.
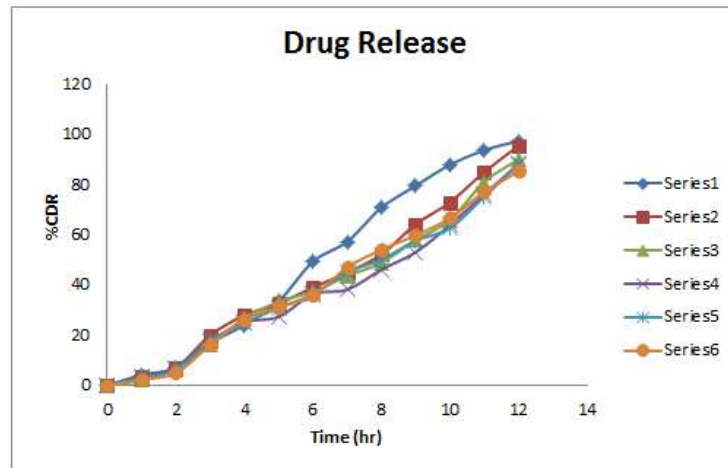

Fig. 3: In-vitro drug release of Sustained Release-matrix tablets of Acyclovir.

Release kinetic studies: As shown in table 3 and fig. 3, according to various kinetic models, were giving linear relationship. In F6 zero order plot (fig. 4A) the best r2 value obtained is 0.973 and first order (fig. 4B) gave 0.915 describing the drug release rate relationship with concentration of drug. Higuchi's equation plot (fig. 4C) (r2 = 0.77) indicating the release of drug from matrix as a square root of time dependent process based on non-Fickian Super Case II type diffusion.

Table No.3: *In-vitro* **drug release kinetic studies of Acyclovir matrix tablet**

Formulation code	Zero order	First order	Higuchi	Korsemyer peppas	n- value
F1	0.936	0.877	0.747	0.984	1.376
F2	0.935	0.776	0.750	0.980	1.336
F3	0.964	0.826	0.758	0.973	1.448
F4	0.965	0.823	0.731	0.985	1.264
F5	0.965	0.856	0.759	0.980	1.316
F6	0.973	0.915	0.770	0.971	1.465
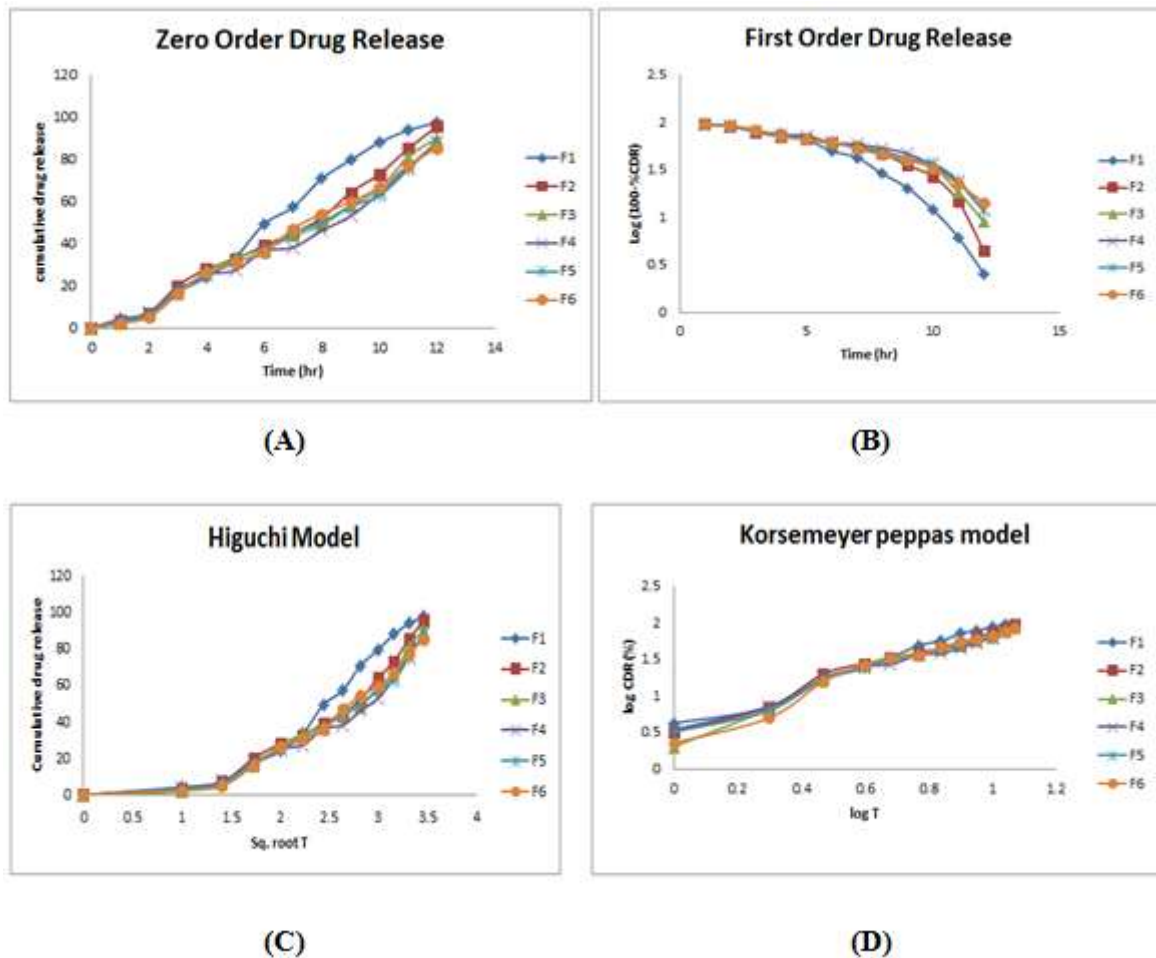
Fig.4: Drug-release kinetic studies (A) Zero order drug release kinetics, (B) First order drug release kinetics, (C) Higuchi model drug release kinetics, (D)Korsemyer peppas model drug release kinetics.

Mechanism of drug release:

By incorporating the first 60% of release data mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxational release, are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion [20]. The value of the release exponent in Acyclovir sustained release matrix tablets obtained as between 1.376 to 1.465, which indicates super case type II diffusion.

Conclusion:

This study indicates the release rate of Acyclovir from matrix tablets formulated by Taro gum could be prolonged and controlled depending on the amount of the natural polymer used. Increasing the amount of the taro gum in the tablets resulted in a reduction in the drug release rate and a linearization of the drug release curve, leading to non-Fickian Super Case II type release mechanism. Drug release could occur both by diffusion and swelling-controlled mechanisms. Drug release kinetics of this formulation corresponds best to zero-order release model and Korsmeyer equation.

References:

1. Modi S.A, Gaikwad P.D, Banker V.H, Pawar S.P, Sustained release drug delivery system: A review, International Journal of Pharmceutical Research & Developement, 2012, 4(3), 147-156.
2. Shoeb MH, Tazeen J, Merchant HA,Yousuf RI, Evaluation of drug release kinetics from Ibuprofen matrix tablets using HPMC, Pakistan Journal of Pharmaceutical Sciences., 2006, 19(2), 119-124.
3. Fahan JA, Sushma D, Smriti K, Sheveta B, Development and evaluation of floating matrix tablets of acyclovir, Research Journal of Pharmaceutical Biological & Chemical Sciences, 2011, 2(4), 547-553.
4. Kusuma. R.., Reddy V., Rao S.., Evaluation of *Colocasia esculenta* Starch as an Alternative Tablet Excipient to Maize Starch: Assessment by Preformulation and Formulation Studies. International Journal of Pharma Sciences and Research. 2015, 6(01): 57-65.
5. R.Nallathambi, V. Gopal, Isolation and Evalution of Mucoadhesive Polymeres From Colocasia Esculenta and Zizipys Jujube, World Journal of Pharmaceutical Research ,2014, 3(2), 2382-2392.
6. Arora G., Malik K. Singh I. Formulation and Evaluation of Mucoadhesive Matrix Tablets of Taro Gum: Optimization Using Response Surface Methodology. Polimery Medycynie. 2011, 41 (2): 23-33.
7. Verma S., Bansal J., Kumar N., Malviya R., Sharma P. Kumar. Iolation and cheeracterization of Mucilage obtained from Trigonella foenum Greacum seed and Tamerindus Indica polymer as a pharmaceutical excipient. Journal of Drug Delivery & Therapeutics. 2014, 4(3): 106-109.
8. Farooq U., Malviya R., Sharma P. Kumar. Extraction and Characterization of Okra mucilage as pharmaceutical Excipient. Academic Journal of Plant Sciences. 2013, 6 (4): 168-172.
9. Yerram C., Shaik F., A. Vikram, Chimmiri P., Chakravarthi R. N. Design and Evalution of Controlled Relese Matrix Tablets of Acyclovir Sodium using Tamarind seed Polymers. Journal of Pharmaceutical Biology. 2012, 2(2): 55-62.
10. Charyulu Narayana R, Patel Kishan, Jose Jobin, Formulation and Evalution Of Acyclovir Matrix Tablet Using Mucoadhesive Polymer , Journal of Drug Delivery & Therapeutics, 2013, 3(5), 52-57.
11. Desu P., G.Vaishnavi, K. Divya, U. Lakshmi. An overview on preformulation studies. Indo-American Journal of Pharmaceutical Sciences. 2015, 2(10):1399-1407.
12. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Delhi: Varghese Publishing House; 2008:P. 293-342.
13. Aulton ME, Wells JI. Pharmaceutics: The Science of Dosage Form Design.2nd ed. London: Churchill Livingstone; 2003: P.133-140.
14. Hadjiioannou TP, Christian GD, Koupparis MA and Macheras PE., New York: Quantitative Calculations in Pharmaceutical Practice and Research, VCH Publishers Inc.; 1993, P.345-348.
15. Bourne DWA. Pharmacokinetics. *In*: Banker GS, Rhodes CT, Modern Pharmaceutics, 4th ed. New York: Marcel Dekker Inc., P.67-92.
16. Higuchi T., Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Sciences., 1963,52: 1145-1149.
17. Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics,1983, 15: 25-35.
18. Korsmeyer RW, Lustig SR and Peppas NA . Solute and penetrant diffusion in swellable polymers. I. Mathematical modeling. Journal of Polymer Science Part B: Polymer Physics,1986a, 24: 395-408.
19. Korsmeyer RW, von Meerwall E and Peppas NA. Solute and penetrant diffusion in swellable polymers. II. Verification of theoretical models. Journal of Polymer Science Part B: Polymer Physics, 1986b, 24: 409-434.
20. Cox PJ, Khan KA, Munday DL and Sujja-areevath J (1999). Development and evaluation of a multiple-unit oral sustained release dosage form for *S*(+)-ibuprofen: preparation and release kinetics. International Journal of Pharmaceutics, 1999,193: 73-84.

✶✶✶✶✶