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Studies on Drug Release Kinetics and Mechanism from Sustained Release Matrix Tablets of Isoniazid using Natural Polymer Obtained from *Dioscorea Alata*

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Abstract : Sustained-release (SR) matrix tablets of Isoniazid and polysaccharide isolated from tubers of *Dioscorea alata,* 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 Korsmeyer equation.
Keywords : Isoniazid, Sustained-release, *Dioscorea alata*, Natural polysaccharide, *etc.*

Introduction:

Sustained release dosage form is defined as well characterized and reproducible dosage form, which is designed to control drug release profile at a specified rate to achieve desired drug concentration either in blood plasma or at target site. This system will provide actual therapeutic control that would be temporal (time related), spatial (site related) or both. Sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility [(1-2)]. 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

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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 [(3)].

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. Isoniazid is an antitubercular drug, with half-life of 1.5-4 hours and requires multiple daily doses to maintain adequate plasma concentration. [(4)]. Therefore present study is aimed investigate the modified release characteristic of Isoniazid using natural polymer.

Material & Methods:

Fresh *Dioscorea alata* tubers were bought from local market for the extraction of the polysaccharide. Acyclovir and Lactose monohydrate was received as a gift sample from Lobachemie pvt.Ltd, 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 *Dioscorea alata*[(5)]: The yam tuber was peeled and weighted. The 500 gm weighed yam was cut into small pieces. Then the yam pieces were blended with 1.5 liter distilled water which contains 0.33 % sodium metabisulphite. The slurry was kept in a beaker for 25 minute, after that supernatant layer was separate in another beaker. The yam mucilage was precipitated from supernatant using Acetone in ratio of 2:1 mixed properly with glassrod. This solution was kept in a Hot air oven at 50 ºC for One hour. Than filter the solution and separate the precipitated mucilage. After filtration it was dried in Hot air oven at 60ºC in petridish for 25 minutes. The dried mucilage was crushed and powdered; the crushed powder put in air tight container. It was characterize for yield, appearance, pH, viscosity flow properties etc [(6)].

Formulation of Sustained Release Matrix Tablet of Isoniazid [(7-8)]: Different tablet formulations were prepared by wet granulation method by the given formula in table no. 1. The drug: polymer ratios are 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5 respectively used. The natural polysaccharide was used as matrix forming material. All ingredients were weighed accurately. Than mixed together for 10 minutes in polybag and mixture was passed. Now wet mass prepared using small quantity of distilled water as a moistening agent. The wet mass was passed through a screen (mesh size 18) and granules were dried in a Hot air oven at 45ºC for 2 hours. When granules were dried again passed to sieve 18.The tablets were compressed using hand operating machine.

Table No. 1: Formulation formulas for matrix tablet

Ingredients	F1	F2	F3	F4	F5
Drug (Isoniazid)	100	100	100	100	100
Polysaccharide (DA)	50	100	150	200	250
Lactose	340	290	240	190	140
Magnesium stearate	5	5	5	5	5
Talc	5	5	5	5	5

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

Tablet Evaluation [8-11]: Tablets were subjected to various precompression and post compression physical tests which include flow properties, weight variation, 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 263 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 263 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 [(12)]. The first order Eq. (2) describes the release from system where release rate is concentration dependent [(13)]. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3) [(14)].

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

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

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

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 [(15-17)]:

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

Where $Mt / M\infty$ are fraction of drug released at time t, k is the rate constant and n is the release exponent, which characterizes 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 light brown in colour (*Dioscorea alata*). The viscosity was found to be 1.1032 cps. The pH was found to be 6.7.

Taro gum was isolated from *Dioscorea alata* (Tubers) and characterized. Percent yield was calculated 9%. Bulk density of taro gum was found to be 0.64g/ml and tapped density was found to be 0.71 g/ml. swelling index of the taro gum was 27 %. Carrs index and hausners ratio was respectively found to be 10.46% and 1.10. Angle of repose of taro gum was found to be 29.68^0.

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 21.3-25.64 its indicate well to passable flow of granules. Compressibility index was found in the range from 11.76 % -16.9 % 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 4.3 to 6.3 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.

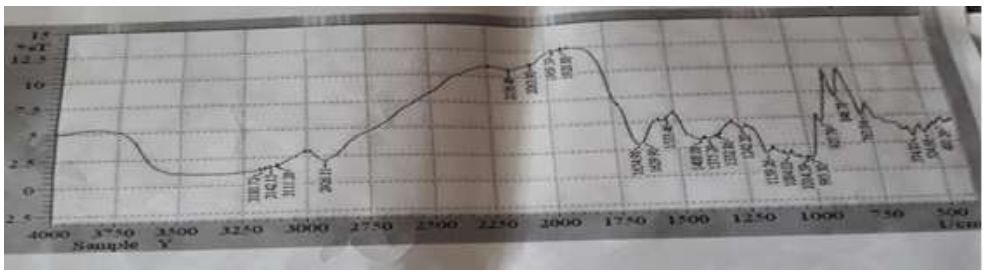
Drug Content (%) -The drug content for all the formulated tablets was found to 96.39% to 99.25 % of Isoniazid (Table 2). It complies with official specifications.

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

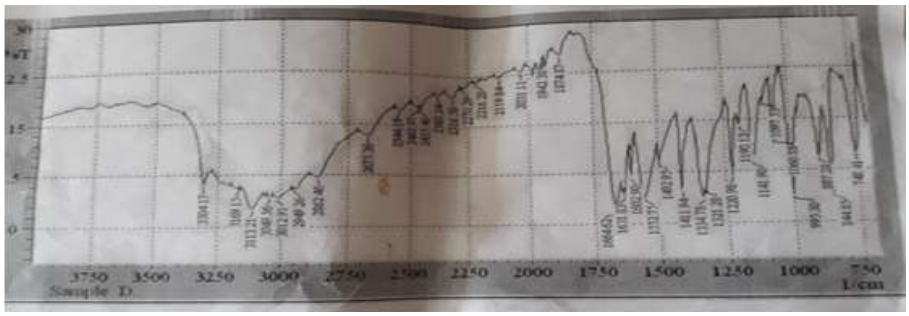
Batch No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Housner Ratio	Angle of Repose (°)	Weight Variation (mg) (n=20)	Hardness kg/cm2 (n=3)	Friability (%) (n=20)	Drug Content (%) (n=3)
F-1	0.51	0.60	15	1.17	21.30	499.33	5.33	0.86	97.38
F-2	0.42	0.50	16	1.19	22.78	502.33	5	0.95	96.39
F-3	0.54	0.65	16.9	1.20	21.80	498.66	4.3	0.93	97.63
F-4	0.60	0.68	11.76	1.13	25.64	499	5.3	0.56	97.5
F-5	0.51	0.60	15	1.17	24.22	498.66	6.3	0.32	99.25

where n is number of Tablets.

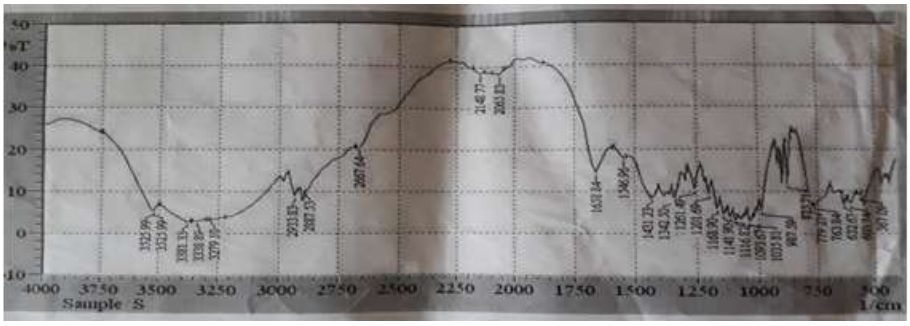
Drug - excipient compatibility study: Compatibility study of drug and Polysaccharide was conducted by employing I.R. Spectral studies. The IR spectrum of Isoniazid, Yam polysacharide and their physical mixtures are shown in Figure The following characteristic peaks were observed with Isoniazid C=N- (stretching) 1602.4 cm^{-1}, C-N- (stretching) 1334.78 cm^{-1}, N-H- (stretching) 3406.1 cm-1,Ring C-C-H system bending at 844.85 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) Isoniazid (B) Yam 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 F5 was studied 69.6%- 72.2 % (Fig.2).

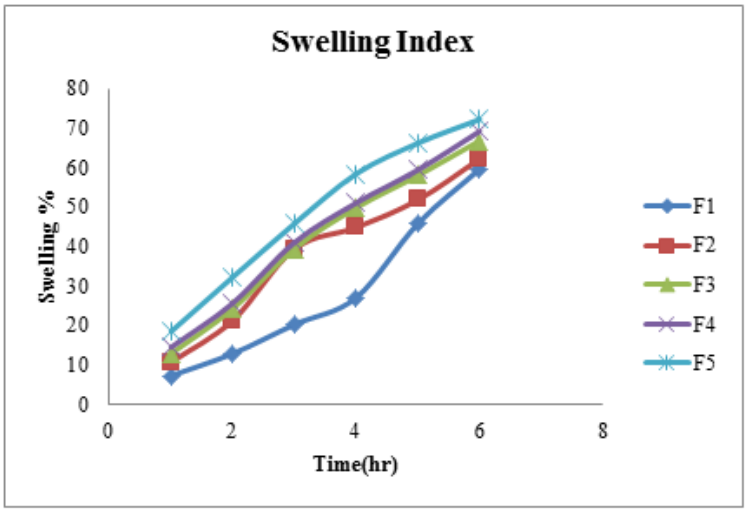


Fig. 2: Swelling behavior of Sustained Release-matrix tablets of Isoniazid.

***In-vitro* drug release study:** *In vitro* drug release profile of the prepared Isoniazid 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 97.24% of drug after 12 hr. The formulation F2 containing 1% of polymer released 95.8% of drug after 12 hr. The formulation F3 containing 1.5% of polymer released 91.12% of drug after 12 hr. The formulation F4 containing 2% of polymer released 88.24% of drug after 12 hr. The formulation F5 containing 2.5% of polymer released 85.54 % 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.

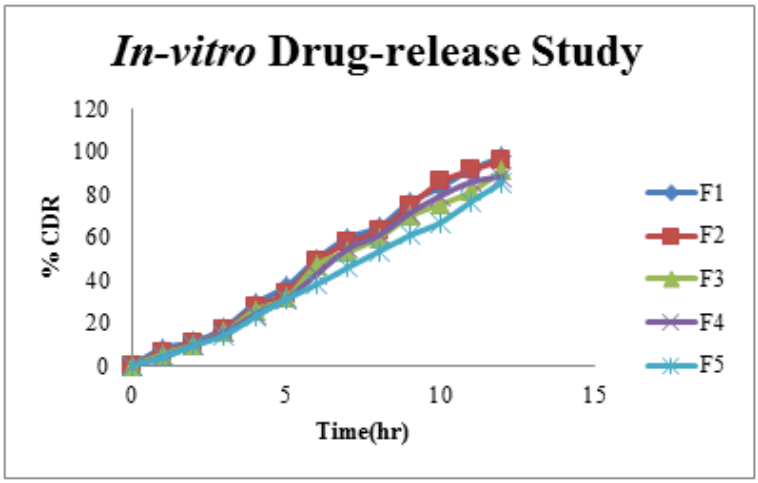


Fig. 3: In-vitro drug release of Sustained Release-matrix tablets of Isoniazid.

Release kinetic studies: As shown in table 3 and fig. 3, according to various kinetic models, were giving linear relationship. In F1-F5 zero order plot (fig. 4A) the r2 value obtained in range of 0.957-0.965 and first order (fig. 4B) gave 0.85-0.943 describing the drug release rate relationship with concentration of drug , increasing the amount polysaccharide to a limit could decline rate of release , further increase in polymer concentration may not effective . Higuchi's equation plot (fig. 4C) (r2 = 0.751-0.778) 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 Isoniazid matrix tablet

S. No.	Batch	Zero order	First order	Higuchi	Korse meyer	n-value
1.	F1	0.957	0.850	0.778	0.982	1.086
2.	F2	0.957	0.879	0.758	0.986	1.195
3.	F3	0.965	0.909	0.768	0.991	1.193
4.	F4	0.964	0.943	0.751	0.996	1.291
5.	F5	0.964	0.913	0.754	0.998	1.250

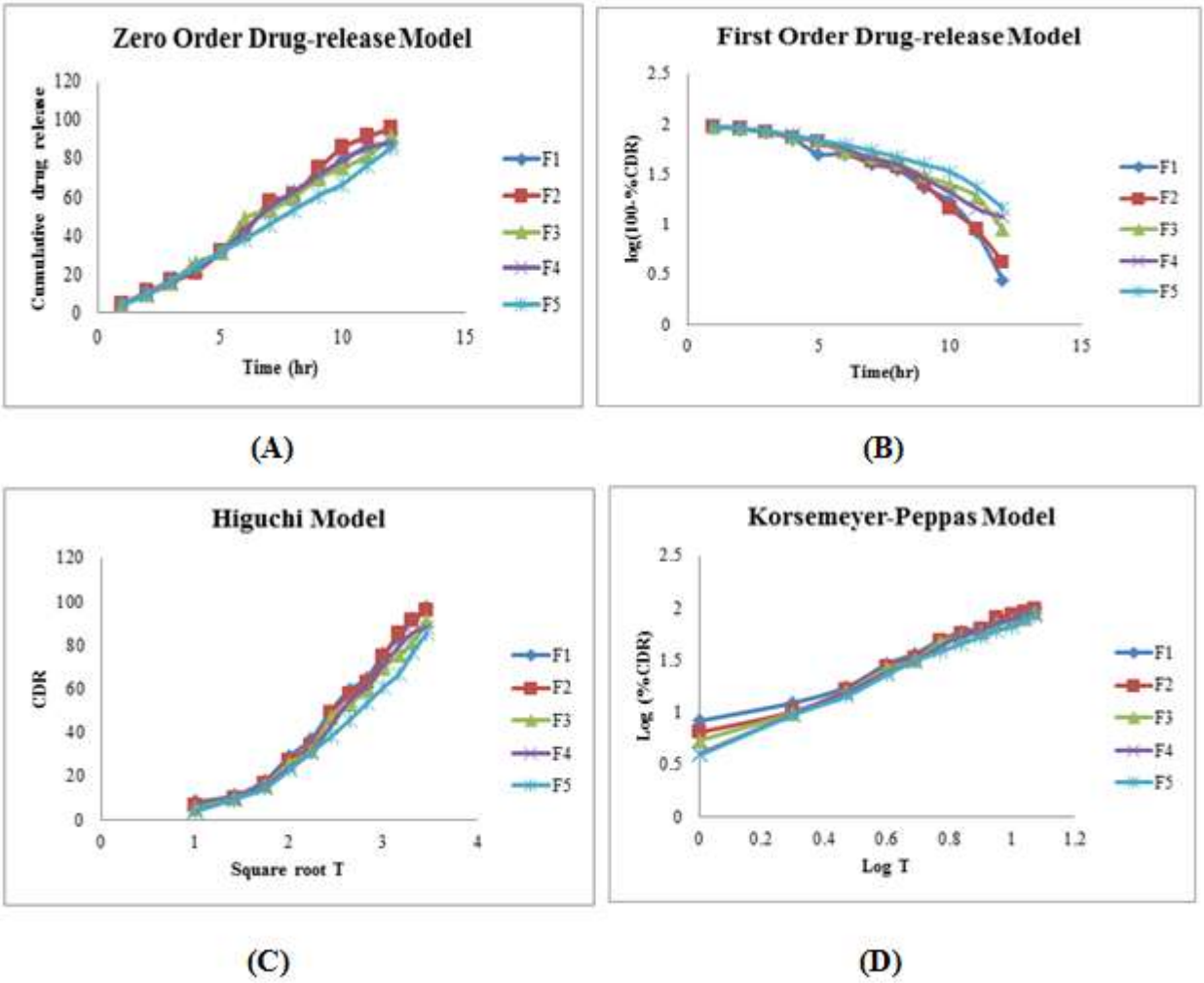


Fig.4: Drug-release kinetic studies (A) Zero order drug release kinetics, (B) First order drug release kinetics, (C) Higuchi model drug release kinetics, (D)Korsemyer peppas model drug release kinetics.

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 super case-II 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.Super Case-II 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 [(18)]. The value of the release exponent in Isoniazid sustained release matrix tablets obtained as between 1.086 to 1.25, which indicates super case type II diffusion.

Conclusion:

This study indicates the release rate of Isoniazid from matrix tablets formulated by Yam polysaccharide could be prolonged and controlled depending on the amount of the natural polymer used. Increasing the amount of the Yam polysaccharide to a limit (Further increase in polymer concentration may no longer effective) 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. The direct relationship was observed between swelling index and concentration of polysaccharide. The concentration of polysaccharide is increases, the swelling behavior increases. Practically, the percent of Cumulative Drug Release decreases with increases in concentration of mucilage and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of polysaccharide. The slow release is because of the formation of a thick gel structure that delays drug release from matrix tablet.

References:

1. Goyal Shagun, Agarwal Gaurav, Agarwal Shilpi, Karar P.K, Oral Sustained Release Tablets: An Overview with a Special Emphasis on Matrix Tablet. American Journal of Advanced Drug Delivery. 2017; 5(2), 64-76.
2. Jaimini Manish, Kothari Abhay, Sustained release matrix type drug delivery system: A Review. Journal of Drug Delivery & Therapeutics. 2012; 2(6), 142-148.
3. 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.
4. Hussain M.D. Zakir, Kumar Kotta Kranthi, Rao V.P., Koteswara V.S. ,K. kanth Sasai, Kumar T.Sai Sravan, Formulation and evaluation of sustained release matrix tablets of Isoniazid. International Journal of Pharmacy and Technology. 2010; 2 (4): 1084-1097.
5. Erebor, J.O Iwuagwu, M.A, Uhumwangho, M.U, Arhewoh, M.I and Oshoma, J,Studies On The Tabletting Characteristics Of Paracetamol Tablets Using Mucilage Extracted From *Dioscorea Alata*; Nig. Journ. Pharm. Sci.,2013; 12(2): 22-29.
6. Farooq Uzma, Malviya Rishabha, Sharma Pramod Kumar, Extraction and Characterization of Okra Mucilage as Pharmaceutical Excipient. Acad. J. Plant Sci., 2013;6 (4) :168-172.
7. Akhtar M. F., Rabbani M., Sharif A., Akhtar B., Saleem A., Murtaza G., Formulation and characterization of modified release tablets containing isoniazid using swellable polymers. Afr J Tradit Complement Altern Med.2011; 8(3) :250-259
8. Suresh. S, Mohammad Zakir Hussain, Saravanan. C, Venkatesh. S, Narayana Swamy V.B., Formulation and evaluation of sustained release matrix tablets of Isoniazid. Scholars Research Library Der Pharmacia Lettre. 2011; (1): 237-246.
9. Desu P., G.Vaishnavi, K. Divya, U. Lakshmi. An overview on preformulation studies. Indo-American Journal of Pharmaceutical Sciences. 2015, 2(10):1399-1407.
10. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Delhi: Varghese Publishing House; 2008:P. 293-342.
11. Aulton ME, Wells JI. Pharmaceutics: The Science of Dosage Form Design.2nd ed. London: Churchill Livingstone; 2003: P.133-140.
12. 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.
13. Bourne DWA. Pharmacokinetics. *In*: Banker GS, Rhodes CT, Modern Pharmaceutics, 4th ed. New York: Marcel Dekker Inc., P.67-92.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.

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