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INFLUENCE OF HYDROPHILIC, HYDROPHOBIC AND PLASTIC POLYMERS ON RELEASE RATE OF ISONIAZID SR TABLETS

Pawar R.G.*, Shinde S.K., Banerjee S.K., Gaikwad D.D., Jadhav S.L., Gadhave M.V.

Department of Pharmaceutics, VJSM's Vishal Institute of Pharmaceutical Education And Research, Ale,
Pune-412411(Maharashtra)

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For Correspondence:

Pawar R.G.

Department of Pharmaceutics,
VJSM's Vishal Institute of
Pharmaceutical Education And
Research, Ale, Pune-
412411(Maharashtra)

E-mail:

shindesachink@rediffmail.com

ABSTRACT

The objective of the present study was to study the effects of hydrophilic, hydrophobic and plastic polymers on release profile of a sustained release matrix tablets of Isoniazid, a highly water soluble drug. Most commonly used method of modifying the drug release is to include it in a matrix system. Matrix tablets of Isoniazide using HPMC, Ethyl cellulose and Kollidon SR, which are hydrophilic, hydrophobic and plastic in nature respectively, were prepared by direct compression process and were subjected to physical characterization and in vitro drug release studies. The results in the present investigation confirm that the release rate of the drug from the polymer matrices is highly influenced by the drug-polymer ratio. The drug release rate was strongly influenced by the type of polymer and the concentration of polymer. Tablets containing Kollidon SR with the active ingredient demonstrated a rapid rate of drug release with an initial burst effect. While tablets containing HPMC and Ethyl cellulose in the matrix tablet prolonged the release of drug with subsequent minimization of burst effect as confirmed by mean dissolution time, T50 and Higuchi release rate data. To analyze the release mechanism Higuchi, Zero-order and First-order model were used.

INTRODUCTION

In the last two decades, many different kind of controlled-release dosage forms have been developed to improve clinical efficacy of drug along with patient compliance. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action. The most commonly used method of modifying the drug release is to include it in a matrix system.^[1,2] The polymer class represents hydrophobic and water-insoluble materials, which are potentially erodible.^[3] While the other group includes polymers those form hydrophilic matrices which develop a highly viscous gelatinous surface barrier which controls the drug release. Liquid penetration into the matrix is the rate-limiting step in such systems.^[4] Tuberculosis kills more people worldwide than any other single infectious disease.^[5] One of the major drawbacks in the use of isoniazid for the treatment of tuberculosis is the severe toxic/adverse effects associated with it.^[6,7] Isoniazid is a first-line drug recommended by World Health Organization (WHO) for the treatment of tuberculosis. The high solubility in the aqueous medium, shorter half-life (1.5 to 4.5 h) and absorption throughout gastrointestinal tract, indicates that it is a better candidate for sustained drug delivery system. During the last few years, various carrier systems, like microparticles, stealth liposome and microspheres have been developed for the sustained delivery of isoniazid for better chemotherapeutic efficacy against tuberculosis.^[8, 9, 10]

MATERIAL AND METHODS

Materials

Isoniazid was a kind gift from Lupin, Aurangabad. HPMC K100M was used as received from The Dow Chemical Company, Michigan. Ethyl cellulose was obtained from Lobachemie Pvt. Ltd., Mumbai. Kollidon SR was used as received from BASF Pvt. Ltd., Mumbai. Dicalcium phosphate and Magnesium stearate were from Central Drug House, New Delhi. Aerosil was obtained from Himedia Laboratories Pvt. Ltd., Mumbai. Potassium dihydrogen phosphate, Disodium hydrogen phosphate and Hydrochloric acid were of analytical grade.

Preparation of matrix tablets

For tablet preparation, method of dry blending of the active ingredients with release retarding agents, release rate modifiers, lubricants and flow promoters followed by direct compression was adopted. Table 1 shows the formulations of matrix tablets. Formulation T1 to T3 contains isoniazide and HPMC K100M while formulations T4 to T6 contain isoniazide along with Ethyl cellulose and formulations T7 to T9 contain isoniazide along with Kollidon SR. Twenty

tablets were prepared for each formulation. The particles were passed through 40 mesh and properly weighed HPMC K100M/Ethyl cellulose/Kollidon SR, Dicalcium phosphate, Magnesium stearate, Aerosil and Isoniazide were blended in a laboratory mixture for 10 minutes. Proper attention has been given to ensure thorough mixing and phase homogenization.

The appropriate amounts of the mixture were then compressed using a RimekKarnavati laboratory hydraulic press equipped with an 8 mm punch and die set. The compression force and compression time were kept at a constant level required to produce tablets of about 8.0-12.0 kg/cm² hardness. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight containers at room temperature for further study.

Table-1: Formulation and Evaluation of Isoniazide sustain release matrix tablets.

Ingredient (mg/tablet)	T1	T2	T3	T4	T5	T6	T7	T8	T9
Isoniazide	100	100	100	100	100	100	100	100	100
Methocel K100M/ Ethyl cellulose/ Kollidon SR	75	105	135	75	105	135	75	105	135
Dicalcium phosphate	119	89	59	119	89	59	119	89	59
Magnesium stearate	3	3	3	3	3	3	3	3	3
Aerosil	3	3	3	3	3	3	3	3	3
Carr's index	20.6	18.64	15.38	16	20	18.5	15	17.5	11.11
Hausner ratio	1.26	1.3	1.18	1.19	1.25	1.22	1.18	1.21	1.2
Hardness	8-11	8-10	9-12	9-11	10-12	8-12	8-11	8-12	9-12
Friability	0.08	0.13	0.15	0.16	0.13	0.18	0.18	0.42	0.21

T1 to T3: HPMC, T4 to T6: Ethyl cellulose, T7 to T9: Kollidon SR

Dissolution studies

In vitro drug release studies from the prepared matrix tablets were conducted for a period of 12 hours using Electrolab's six station USP XXII type 1 apparatus at $37 \pm 0.5^\circ\text{C}$ and 75 rpm speed. The dissolution studies were carried out in triplicate for 12 hours (initial 2 hours in simulated gastric fluid and rest 10 hours in phosphate buffer of pH 6.8). At every 1-hour interval, samples of 10 ml were withdrawn from the dissolution medium and replaced with fresh dissolution medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed for isoniazide by double beam UV spectrophotometer (Perkin Elmer, USA) at 263 nm. The amounts of drug present in the

samples were calculated with the help of appropriate calibration curves constructed from isoniazide reference standard. Drug dissolved at specified time periods was plotted as percent release versus time (hours) curve. This drug release profiles were fitted into several mathematical models to get an idea about the release mechanism of isoniazide from the matrix tablets.

Analysis of Release Profiles

After completing in vitro dissolution of all the batches for twelve hours, the data was treated with zero order^[11], Higuchi^[12] and First order^[13] equations (equation 1-3 respectively).

$$M_t = M_0 + k_0t \quad (1)$$

$$M_t = M_0 - k_H t^{1/2} \quad (2)$$

$$\ln M_t = \ln M_0 - k_1 t \quad (3)$$

In these equations, M_t is the cumulative amount of drug released at any specified time (t) and M_0 is the dose of the drug incorporated in the delivery system. k_0 , k_H and k_1 are rate constants for zero order, Higuchi and first order model respectively.

RESULTS AND DISCUSSION

The plasma half-life in patients with normal renal and hepatic function is 1 to 4 hours, depending on the rate of metabolism; it is 0.5 to 1.6 hours in fast acetylators and 2 to 5 hours in slow acetylators.^[14, 15] Isoniazid has been shown to be well absorbed throughout the length of the gastrointestinal tract and produce peak plasma concentration within 2 hours. The use of rapid release oral isoniazid preparation has been declined due to the higher incidence of side effects resulting from rapid absorption. Isoniazid has a short elimination half-life, which also encourages the drug to be formulated in sustained release dosage form. Due to its rapid elimination and narrow therapeutic index, this drug is indeed a suitable candidate to be formulated into sustained release dosage forms.

Effect of physico-chemical property of drug on release rate

The effect of physico-chemical property of drug molecule on release retarding ability of Kollidon SR, Ethyl cellulose and HPMC at 45%, 35% and 25% polymeric content is illustrated in Fig. 1 - 3, respectively. Release rates of isoniazid was found to be significantly different from each specific class of polymer. This indicates that the release retarding efficiency of the polymers critically depends on the physicochemical nature of the drug molecule. Fig. 1-3 shows that, at any particular polymeric level, Ethyl cellulose can exert the highest drug retarding effect on isoniazid. Release of isoniazid was highest from HPMC matrix tablets. Formulation T-1 and T-3 containing 25% and 45% of Kollidon SR released

97% and 87 % of isoniazid respectively after 12 hours. However a burst release of isoniazid was observed with formulation T-7, T-8 and T-9. About 45% of drug was released from T-7 within the two hour of dissolution period. Ethyl cellulose imparted stronger retardation over drug release than that of HPMC. Although the drug release rates from Ethyl cellulose and HPMC matrices were significantly different.

This disparity in release rate of different classes of drugs can be attributed to the differences in their physical and chemical properties particularly on the solubility profile.^[16] Drug particles present in the surface of the matrix is initially released into the surrounding media producing many pores and cracks which facilitates further release of drug. Isoniazid is a basic drug having a pKa value of 9.5 and the molecule is freely soluble in water. Alderman reported that, the release kinetics of hydrosoluble drugs is mainly governed by diffusion from hydrophilic matrice.^[17] Isoniazid present in the surface of Kollidon SR matrix tablet rapidly leaves the matrix system because of its basic nature. The burst effect observed with isoniazid from formulations T-7 to T-9 can be attributed to rapid ionization and higher solubility of isoniazid in acidic medium as well as the non-swellable property of Kollidon SR.

Effect of Polymeric content on the release profile of drugs

The effect of polymer content on drug-release as a function of time was found to be significantly different for a specific set of drug and polymer irrespective of their chemical nature. Comparing the corresponding release profile for a particular drug and polymer system from Figure 4, it can be observed that, for all the drugs under investigation, drug release is inversely proportional to the level of rate retarding polymer present in the matrix system, i.e. the rate and extent of drug release decreases with increase in total polymeric content of the matrix. It is observed that, for Kollidon SR matrix system, 93%, 86% and 79% of isoniazid was released from formulations containing 25, 35 and 45 % of Kollidon SR respectively. Although the release rates were different, similar trend was found when Ethyl cellulose and HPMC-100 cps were used as the matrix-forming polymer. Such increase in the polymer content results in a decrease in the drug release rate due to a decrease in the total porosity of the molecule.^[18]

Effect of polymer type on the release profile of drugs

The class and nature of the matrix forming polymers prejudiced the release profile of active ingredient. Types of polymers used to prepare the matrix were also found to reveal differential effect on matrix disintegration. Ethylcellulose based matrix tablets did not show any disintegration after 12-hours of dissolution period irrespective of polymer content. On the

other hand, formulations containing 25% Kollidon SR disintegrated after 10 hours while matrix system loaded with 25% HPMC disintegrated after 8 hours leaving a gel-like mass. Disintegration time was found to be independent of physico-chemical property of the active ingredient. Proportion of filler in the matrix and chemical nature of the rate retarding agent imparted the governing effect on matrix disintegration. The effect of polymer type on drug-release as a function of time can be seen by comparing the corresponding release profile of a particular drug from any matrix system at a particular polymeric level in Fig. 1-3. The overall rate of release of a particular drug at a specific polymeric content was again found to be significantly varied for various polymers. Irrespective of chemical nature of the drugs; it was found that, the release is highest from HPMC-100 cps matrix whereas lowest drug release was found with Ethyl cellulose system. At 45% polymeric content, 73%, 79% and 86% of isoniazid was released from Ethyl cellulose, Kollidon SR and HPMC-100 cps matrix system after 12 hour of dissolution period. On the other hand, at 25 % polymeric load, 87, 93 and 97 % of the same drug was released from the above mentioned matrix systems respectively after 12-hour.

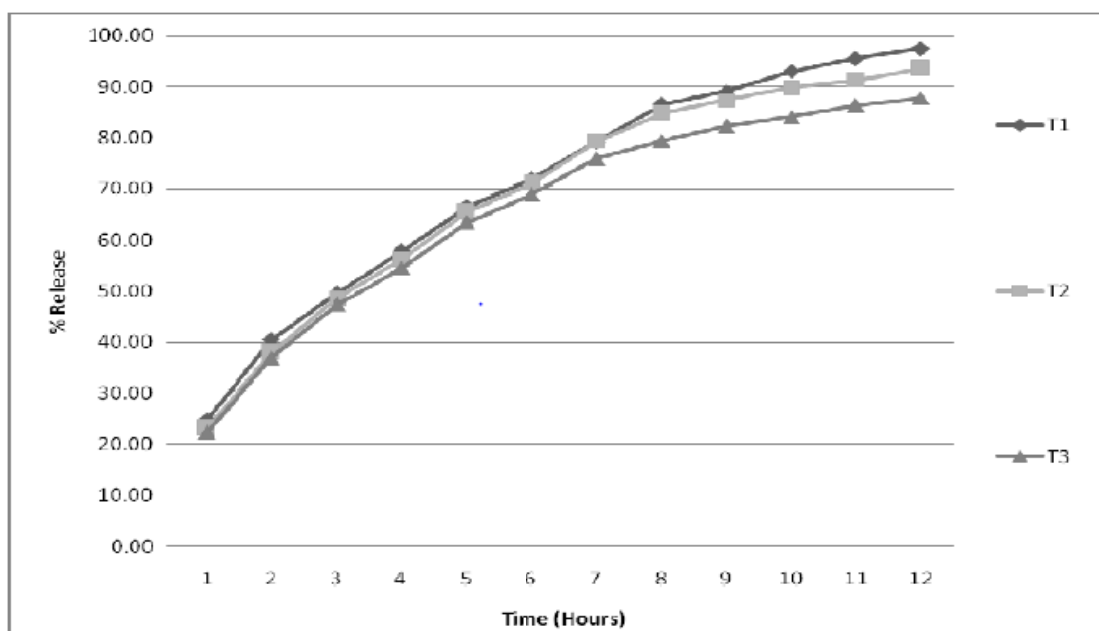


Figure-1: Percent of drug release from matrix tablets containing (a) 75 mg (b) 105 mg and (c) 135 mg HPMC – 100cpsin dissolution study at pH 1.2 and 6.8 (n=3).

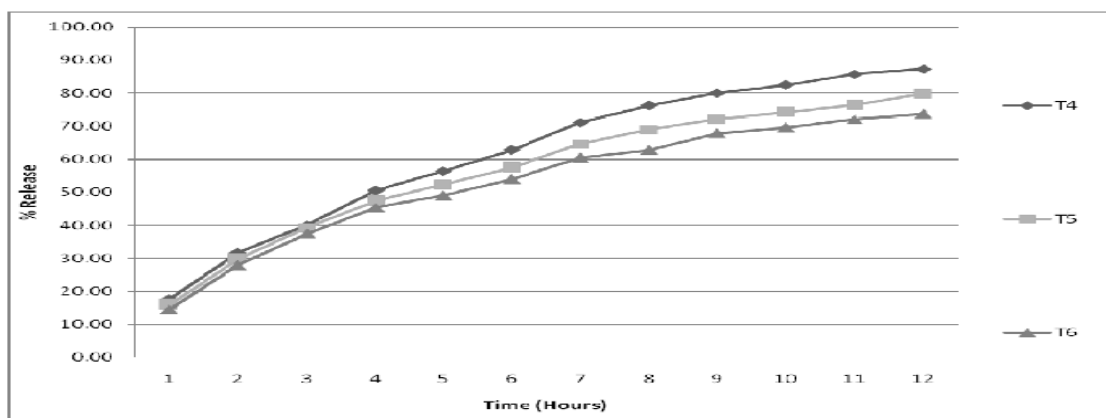


Figure-2: Percent of drug release from matrix tablets containing (a) 75 mg (b) 105 mg and (c) 135 mg Ethyl cellulose in dissolution study at pH 1.2 and 6.8 (n=3).

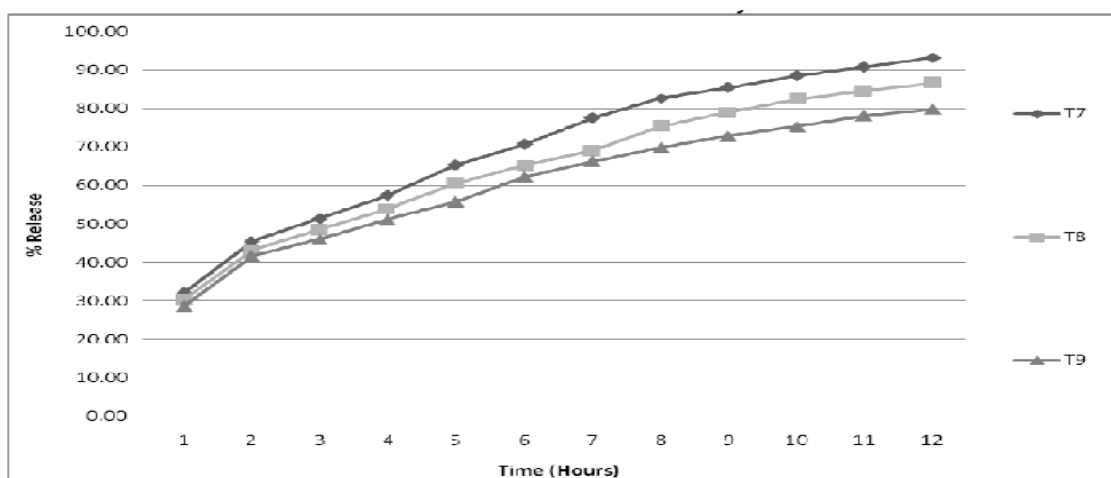


Figure-3: Percent of drug release from matrix tablets containing (a) 75 mg (b) 105 mg and (c) 135 mg Kollidon SR in dissolution study at pH 1.2 and 6.8 (n=3).

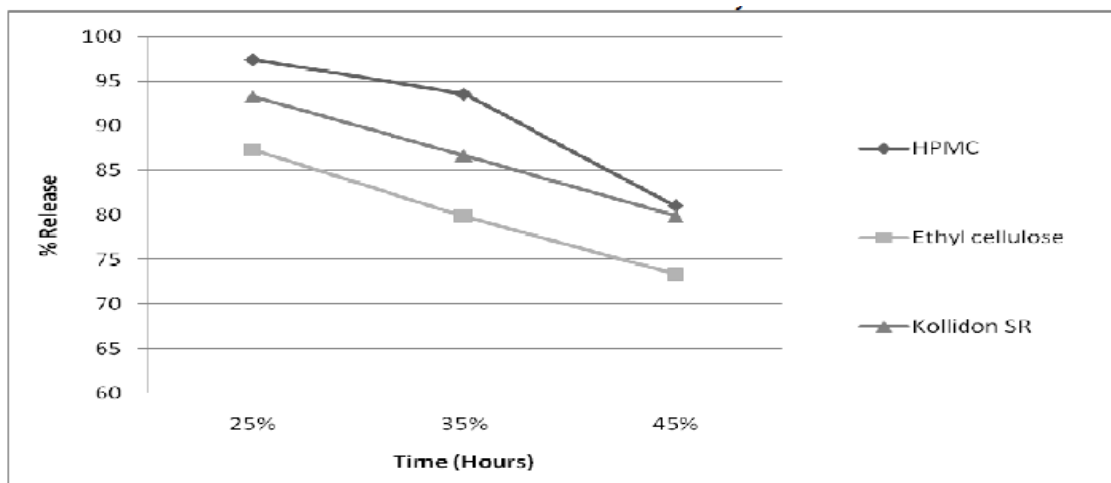


Figure-4: Effect of HPMC, Ethyl cellulose and Kollidon SR level on release rate.

The rate and extent of drug release was found highest with HPMC-100 cps polymeric systems. Similar results were obtained by Nokhodchi et al.^[19] Additionally, HPMC also imparted a more controlled influence on the release pattern of all drugs with reduction and/or elimination of the chances of burst release. The fact can be credited to the hydrophilic nature of HPMC. When exposed to the media, the solvent penetrates into the free spaces between macromolecular chains of HPMC. After solvation of the polymer chains, the dimensions of the polymer molecule increase due to the polymer relaxation by the stress of the penetrated media. This phenomenon is defined as swelling and it is characterized by the formation of a gel-like network surrounding the tablet. This swelling and hydration property of HPMC causes an immediate formation of a surface barrier around the matrix tablet that diminishes the chances of burst release.

Release Kinetics

The values of rate constant (k) and correlation coefficient (r²) for zero order, first order and Higuchi equation are presented in Table 2.

Table-2: *In-vitro* release kinetics parameters of Isoniazid from the matrix tablet.

Code	Zero order		First order		Higuchi	
	r ²	k	r ²	k	r ²	K
T1	0.910	0.122	0.965	-0.127	0.970	19.77
T2	0.898	0.118	0.995	-0.099	0.982	29.34
T3	0.882	0.110	0.993	-0.074	0.976	26.96
T4	0.928	0.114	0.997	-0.075	0.990	29.27
T5	0.916	0.102	0.994	-0.055	0.988	25.70
T6	0.911	0.094	0.987	-0.046	0.985	23.93
T7	0.878	0.109	0.990	-0.090	0.992	25.38
T8	0.877	0.100	0.995	-0.065	0.995	23.06
T9	0.859	0.090	0.996	-0.049	0.992	20.64

CONCLUSION

At present, all the polymers being studied are used extensively in pharmaceuticals to control the release of drug. The approach of the present study was to make a comparative evaluation among these polymers and to assess the effect of physico-chemical nature of the active ingredient on drug release profile. The study reveals that, the release of water soluble drugs was higher than the drugs with lower solubility and the mechanism of release was changed with the nature and content of polymer in the matrix. The type of polymers used imparts a conspicuous effect on release mechanism. The data generated in this study also shows that, the drug release from plastic and hydrophobic matrix was less than hydrophilic polymer. Isoniazid sustained release matrix tablet was prepared successfully using HPMC, Ethyl

cellulose and Kollidon SR as polymer to retard release and achieve required dissolution profile. Drug release kinetics of this formulation correspond to 1st order and Higuchi's model. Drug release mechanism cannot be predicted clearly as it appears to be a complex mechanism of swelling, diffusion and erosion.

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