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Research Article

FORMULATION OF SUSTAINED RELEASE MATRIX TABLETS OF ISONIAZID BY USING DIFFERENT POLYMERS

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ABSTRACT

Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Isoniazid is an antitubercular, with half life of 1.5-4 hours and requires multiple daily doses to maintain adequate plasma concentration. The present study was aim to formulate the sustained release oral matrix tablet by using isoniazid as a model drug and see the effects of different polymers. Various formulations of sustained release tablets of isoniazid were developed using various polymers Guargum, Carbopol, Tragacanth Gum and PEG-6000, in different proportion and combinations. IR spectra studies revealed that the drug and polymers used were compatible. In further studies the tablets were evaluated for physical characterization, *in vitro* swelling behavior, *in vitro* release study and stability studies.

Keywords :-Antitubercular, Isoniazid, Sustained release, Matrix system.

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INTRODUCTION

Among the drugs that are administered orally, solid dosage form represents the preferred class of product. Solid dosage form provides best protection to the drug against temperature, humidity, oxygen, light and stress during transportation and also ensures accuracy of dosage, compactness, portability, blandness of taste, and ease of administration [1]. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time [2]. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action [3], timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose [4, 5]. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT [6].

Matrix system

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 [7]; it is release system for delay and control of the release of the

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drug that is dissolved or dispersed in a resistant supports to disintegration [8]. To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms.

The therapeutic efficacy of drug under clinical conditions is not simply a function of its intrinsic pharmacology activity but also depends upon the path of the drug molecule from the site of administration to the target site. Different conditions encountered by the drug molecule while traversing the path of distribution may alter either the effectiveness of the drug or affect the amount of the drug reaching the receptor site [9-12].

EXPERIMENTAL METHODS

Characterization of Drug

Physical description

Isoniazid: Colourless, odourless, white crystalline powder.

Solubility

Water - 1 g in 8g water

Ethanol - 1 g in 50 ml alcohol

- Slightly soluble in chloroform and very slightly soluble in ether.

Identification Test (Isoniazid)

- Dissolve 0.1g in 2ml of water, add a warm solution of 0.1g of vanillin in 10ml of water, allow to stand and scratch the inside of the container with a glass rod; a yellow precipitate is produced. The resulting range of the precipitate, after recrystallization from 5ml of ethanol (70%) and drying at 105^0C [13].
- Infrared absorption spectrophotometry.

Method of Analysis

Method of quantitation of Isoniazid by U. V. Spectroscopy.

U.V. Scan

A solution of Isoniazid was prepared and scanned for UV absorption. The solution of Isoniazid showed maximum UV absorption at 263 nm was shown in table 1.

Preparation of 0.1 N HCl

Dilute 8.5 ml of concentrated HCl in 1000 ml of distilled water to get 0.1 N HCl.

Preparation of phosphate buffer pH 6.8

Preparation of 0.2 M potassium dihydrogen phosphate solution-Dissolve 27.213 g of potassium dihydrogen phosphate in 1000 ml of distilled water to get 0.2 M potassium dihydrogen phosphate.

Preparation of 0.2 M sodium hydroxide solution- Dissolve 8.0 g of sodium hydroxide pallets in 1000 ml of distilled water.

Weigh accurately 2 g of sodium hydroxide in a 250ml of distilled water and weigh 6.8 g of potassium dihydrogen phosphate in a 250ml of distilled water from 250ml of sodium hydroxide solution take 112 ml of solution in a 1000ml beaker and add 250ml of potassium dihydrogen phosphate to 1000ml beaker and make the final volume to 1000ml with water [14].

Preparation of Stock solution

An accurately weighed 100 mg of Isoniazid was dissolved in 100 ml of phosphate buffer of pH 1.2, Ph 6.8, to get solutions of 1000 µg/ml. From this 10ml of solution was withdrawn and diluted upto 100 ml with phosphate buffer to get Isoniazid stock solution of 100µg/ml.

Preparation of Standard solutions

From above stock solutions aliquot of 10, 20, 30, 40,upto 100 ml were withdrawn and diluted to 100ml with phosphate buffer pH 1.2, and pH 6.8 to get concentration range of 10-100 µg/ml, for Isoniazid

Preparation of standard Curve

The absorbance of standard solutions prepared above was measured at λ_{max} 263nm for Isoniazid. The data so obtained was plotted for concentration in X axis and absorbance in Y axis and regression was carried out and shown in table 2 and fig 1 [14].

POLYMER PROFILE

Guar gum

The USPNF20 describes guar gum as a gum obtained from the ground endosperms of *Cyamopsis tetragonolobus* (L) Taub. (family-Leguminosae). It consist chiefly of high molecular weight hydrocolloidal polysaccharide, composed of gallactan and mannal units combined through glycoside linkages, which may be described chemically as a Galactomannam. The pHEUR2002 similiarly describes guargallactomannan.as being obtained from the seeds of Cyamopsis *tetragonolobus* (L) Taub by grinding the endosperms and subsequent partial hydrolysis. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol. The optimum rates of hydration occur at pH 7.5-9.0. Finely milled powders swell more rapidly and are more difficult to disperse. Two to four hours in water at room temperature are required to develop maximum viscosity [15].

Tragacanth gum

The USPNF 19 describes tragacanth gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt. Tragacanth gum occur as flattened, lammellated, fragments, or as straight

or spirally twisted linear pieces from 0.5-2.5 mm in thickness: it may also be obtained as a powder form. White to yellowish in color, Tragacanth is a transceunt, odourless substance, with aninsipid mucilaginous taste.Practically insoluble in water, ethanol (95%), and other organic solvents. Although insoluble in water, tragacanth gum swells rapidly in 10 times its own weight of either hot or cold water to produce viscous colloidal sols or semi gels [16].Tragacanth dispersion is most stable at pH 4-8, although stability is satisfactory at higher pH or low at pH 2.

Polyethylene glycol

The USPNF 20 describes Polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycolgrades 200-600 are liquids; grades 1000 and above are solids at ambient temperatures. Liquid grades (PEG 200-600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste; PEG600 can occur as a solid and at ambient temperatures. Solid grades (PEG.1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor; grades of PEG 6000 and above are available as free-flowing milled powders [17]. The chemical reactivity of polyethylene glycol is mainly confirmed to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by auto oxidation Liquid and solid polyethyethylene glycol grades may be incompatible with some coloring agents.

Carbomer

Carbomer is acryl acid polymer and mainly used in liquid or semisolid pharmaceutical formulations as suspending, viscosity enhancer, and also used in tablet binder. Carbomers are stable, hygroscopic materials that may be heated at temperatures below 1040 C for up to 2 hours without affecting their thickening efficiency. However, exposure to excessive temperatures can results in discoloration and reduced stability. Carbomer powder should be stored in an airtight, corrosion resistant container in a cool, dry place [18].

EXCEPIENTS

Lactose

It occurs in three forms: α-monohydrate, α-anhydrous, β-anhydrous. Commercial lactose is mainly the α-monohydrate. It is practically insoluble in chloroform, ethanol and ether .soluble in 1in 4.63parts of water.Store in a well-closed container to prevent absorption of moisture. Under humid conditions mold growth may occur. Lactose may develop brown coloration on storage. This reaction is accelerated by warm-damp conditions. A maillard type condensation is likely to occur between lactose and compounds with a primary amino group to form brown colored products. This reaction occurs more rapidly with amorphous then crystalline lactose. It is used as filler, diluent in pharmaceutical preparation [19].

Starch

Starch occur as an odourless and tasteless fine, white-colored powder comprising very small spherical or ovoid granules whole size and shape are characteristic for each botanical variety. Practically insoluble in cold ethanol (95%) and in cold water. Starch swells instantaneously in water by about 5-10% at 37^0C polyvalent cation produce more swelling than monovalent ions, but pH has little effect. Dry, unheated starch is stable if protected from humidity. When used as a diluent or disintigrant on solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties. Starch should be stored in an air tight container in a cool, dry place. A maillard type condensation is likely to occur between starch and compounds with a primary amino group to form brown colored products [22].

Talc

It is hydrous magnesium silicate may contain a small amount of aluminum silicate and iron. Insoluble in water, organic solvents, cold acids and dilute alkalis. Incompatible with quaternary ammonium compounds, Observe normal precautions appropriate to the circumstances and the quantity of the material handled. Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis. Eye protection, gloves, and a respirator are recommended [21].

Magnesium Stearate

Fine, white, precipitated or milled, impulpable powder of low bulk density. Odour and taste are slight but characteristic. The powder is unctuous, and readily adheres to the skin. Stable, non-self-polymerizable, store in a cool, dry place in a well-closed container. Incompatible with strong acidic substances, alkaline substances, iron salts, avoid mixing with strong oxidizing materials [21]. Use with caution with drugs, which are incompatible with alkali. Application in pharmaceutical formulation or technology: Tablet and capsule lubricant, glidant or antiadherent (0.25 – 2.0%).

Determination of bulk density and tapped density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured, then the graduated

cylinder was closed with lid, set into the density determination apparatus (bulk density apparatus, electro lab, Mumbai). The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the following formulas.

Bulk density = W/V_o

Tapped density = W/V_f

Where,

V_o = initial volume

V_f = final volume.

Compressibility index

The *Compressibility index*and*Hausner ratio* are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the *Compressibility Index* and the *Hausner Ratio.*The compressibility index and Hausner ratio may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows:

$$\text{Compressibility index} = \frac{\rho_{Tapped} - \rho_{bulk}}{\rho_{Tapped}}$$

Loss on drying

Determination of loss on drying of granules is important drying time during granulation was optimized depending LOD value. LOD of each batches were tested at 105^{o}c for 2.5 minutes by using "Sartorius" electronic LOD apparatus.

Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

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

$$\theta = \tan^{-1} h/r$$

Where h = height of pile, r= radius of the base of the pile, θ = angle of repose

RESULTS

Table 1. Calibration data of Isoniazid in buffer solution (pH 1.2) at λ_{max} of 263nm

Serial no	Concentration (mcg/ml)	Absorbance(nm)
1	10	0.087
2	20	0.178
3	30	0.260
4	40	0.340
5	50	0.425
6	60	0.510
7	70	0.594
8	80	0.673
9	90	0.749
10	100	0.836

Table 2. Calibration data of Isoniazid in phosphate buffer solution (pH 6.8) at λ_{max} of 263 nm.

Serial no	Concentration	Absorbance(nm)
1	10	0.063
2	20	0.116
3	30	0.170
4	40	0.235
5	50	0.296
6	60	0.351
7	70	0.444
8	80	0.503
9	90	0.567
10	100	0.637

Table 3. Preformulation studies

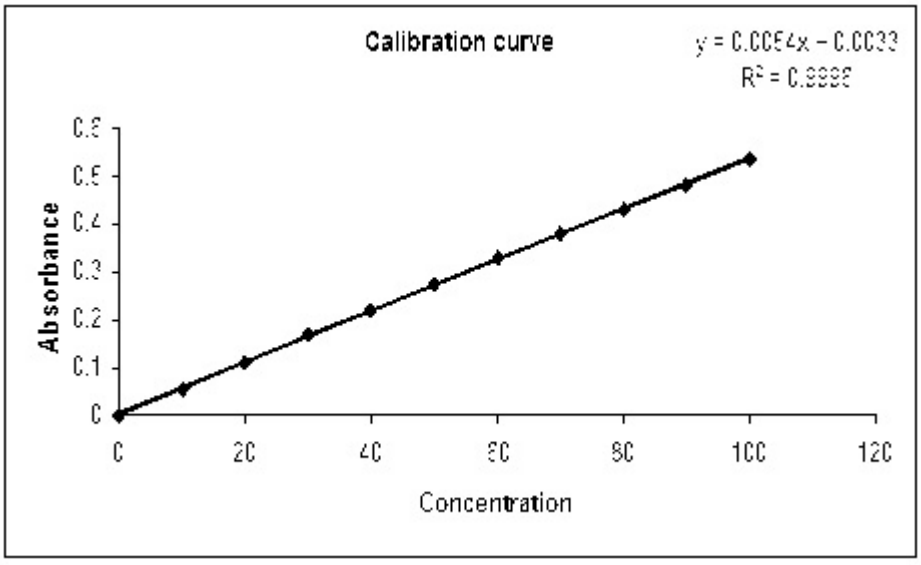
Parameters> Batch	Bulk Density	Tapped Density	Carrs Index	Hausners Ratio	Angle Of Repose(degree)
F 1	0.442	0.638	7.22	1.08	18.10±0.03
F 2	0.522	0.513	7.29	1.10	18.19±0.06
F 3	0.510	0.601	7.31	1.04	19.51±0.057
F 4	0.521	0.711	7.63	1.06	20.33±0.042
F 5	0.560	0.730	7.59	1.14	21.494±0.02
F 6	0.493	0.513	7.86	1.09	21.11±0.026
F 7	0.591	0.509	8.30	1.12	23.962±0.01
F 8	0.601	0.600	8.14	1.15	18.21±0.02
F 9	0.630	0.609	9.11	1.11	24.14±0.042
F 10	0.616	0.510	11.62	1.00	24.18±0.41
F 11	0.592	0.611	13.60	1.18	20.64±0.026
F 12	0.660	0.731	13.11	1.13	24.13±0.042

Table 4. Formulation of isoniazid matrix tablet

Batch > ingredients	F1	F 2	F3	F 4	F 5	F 6	F 7	F 8	F 9	F10	F11	F 12
Drug	100	100	100	100	100	100	100	100	100	100	100	100
Guar gum	100	150	200	-	-	-	-	-	-	-	-	-
Tragacanth- gum	-	-	-	100	150	200	-	-	-	-	-	-
PEG-6000	-	-	-	-	-	-	100	150	200	-	-	-
Carbopol-934p	-	-	-	-	-	-	-	-	-	100	150	200
Magnesium-Stearate	7	7	7	7	7	7	7	7	7	7	7	7
Talc	7	7	7	7	7	7	7	7	7	7	7	7
Starch	21	21	21	21	21	21	21	21	21	21	21	21
Compressible Lactose	115	65	15	115	65	15	115	65	15	115	65	15

Each quantity mentioned will be taken in mgs
Total weight of the tablet = 350mg
Each tablet contains= 100mg of the drug

Fig 1. Calibration curve of Isoniazid in phosphate buffer pH 6.8



SUMMARY AND CONCLUSION

Oral route of drug administration is oldest and safest mode of drug administration. It possess several advantage. It provides accurate dosing without assistantship of administration. In conventional oral drug delivery system, there is little or no control over release of drug, and effective concentration at the target site can be achieved by administration of grossly excessive dosage form. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal.

Isoniazid is an antitubercular agent, with half life of 1.5-4 hours and requires multiple daily doses to maintain adequate plasma concentrations. So it is selected to prepare a sustained release tablet. The objective of this present study is to develop a sustained release tablet of Isoniazid which releases the drug in a sustained manner over a period of 12 hours, by using different polymers and study on polymer concentration effect on release pattern.

The present study was undertaken with an aim to formulate Isoniaizd sustained release tablets using different polymers as release retarding agent. Preformulation study was done initially and results directed for the further course of formulation. Based on Preformulation studies different batches of Isoniazid were prepared using selected excipients. IR spectra studies revealed that the drug and polymers used were compatible. Various formulations of sustained release tablets of Isoniazid were developed using various polymers viz, Guar gum, Tragacanth Gum, PEG-6000 and Carbopol in different proportions and combinations by direct compression technique and the result was shown in table 3 and 4. In further studies the tablets were evaluated for physical characterization, *in vitro* swelling behavior, *in vitro* release study and stability studies.

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Nil

CONFLICT OF INTEREST

No interest

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