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Formulation and evaluation of magnesium sustained release tablets

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ABSTRACT

Sustained release drug delivery is more preferred because they are more advantageous than other dosage forms. The main objective of this present study is formulate and evaluate sustained release magnesium tablets to monitor the reduction in side effects, cure, control of condition by using less quantity of drug. Sustained release matrix tablets of magnesium were formulated using different concentrations of hydroxyl propyl methyl cellulose by using the wet granulation technique. Formulations F1, F2, F3, F4, F5 and F6 shows sudden drug release and F7 shows drug release in sustained manner which contains 25% concentration of HPMC k100M. So HPMC k100M will acts as better sustaining ingredient. And this formulation follows the zero order and higuchi model drug release kinetics.

Keywords: Magnesium chloride, Sustained release tablets, HPMC k100M.

1. INTRODUCTION

Most conventional drug products, such as tablets and capsules are formulated to release the active drug immediately after administration to obtain rapid and complete systemic drug absorption.

The goal of any drug delivery system is to provide a therapeutic concentration of drug to the proper site in desired concentration.

1.1. Controlled drug delivery systems

These systems deliver the drug at the absorption site at a controlled rate.

Controlled drug release can be achieved, by following classes of controlled drug delivery system.

A) Diffusion controlled system

B) Dissolution controlled system

C) Methods using ion-exchange resins

D) Methods using osmotic pressure

E) pH independent formulations

F) Altered density formulations

1.2. Matrix Tablet

Introduction of matrix tablets as a sustained release has given a new break through for novel drug delivery system (NDDS) in the field of pharmaceutical technology. It excludes complex production procedures such as coating and pellitization during manufacturing and drug release rate from dosage form is controlled mainly by the type and proportion of polymer used in preparation. Historically, the most popular drug delivery system has been the matrix because of its low cost and eases of fabrication. Methods of altering the kinetics of drug release from the inherent first order behaviour especially to achieve a constant rate of drug release from matrix devices have involved several [1-17].

There are three types of matrix tablets i.e.

- Hydrophilic matrices
- Fat-wax matrices
- Plastic matrices

1.3. Hydrophilic matrix system

Drug delivery technologists usually tend to consider all hydrophilic delivery systems as hydro gels. Hydro gels are hydrophilic macromolecular networks that after swelling maintain their shape due to permanent links. Very high water content and special surface properties of swollen form give them the ability to simulate natural tissues. The most widely used polymers for drug delivery control; particularly in oral applications are swellable polymers. NaCMC, hydroxymethyl cellulose, polyethylene oxide, polyvinyl pyrolidone and natural gums can be used as matrix materials. The matrix may be

tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix material. Upon immersion in water the hydrophilic matrix quickly forms a gel layer around the tablet. Drug release is controlled by the gel diffusional barrier and /or tablet erosion [2].

1.4. Preparation of Matrix Tablet

The matrix tablet can be prepared by direct compression and granulation and compression. Generally in preparation of matrix tablet, granulation is preferred because of problems like flow, density and compressibility.

The three commonly used granulation methods include wet granulation, dry granulation, melt granulation. These methods are categorized based on the type of binder and the process employed during granulation.

- Wet granulation
- Dry granulation
- Direct compression technique

1.5. Drug profile

1.5.1. Magnesium chloride

Magnesium chloride is essential mineral supplement used to prevent and treat low amounts of magnesium in the blood. Magnesium is very important for the normal functioning of cells, nerves, muscles, bones, and the heart.

Magnesium is a mineral that present in relatively large amounts in the body. Magnesium is important in more than 300 chemical reactions that keep the body working properly. People get magnesium from their diet, but sometimes magnesium supplements are needed if magnesium levels are too low.

Foods that are high in fiber are generally high in magnesium. Dietary sources of magnesium include legumes, whole grains, vegetables (especially broccoli, squash, and green leafy vegetables), seeds, and nuts (especially almonds). Other sources include dairy products, meats, chocolate, and coffee. Water with a high mineral content, or "hard" water, is also a source of magnesium.

Magnesium is also used as a laxative for constipation and for preparation of the bowel for surgical or diagnostic procedures. It is also used as an antacid for acid indigestion and also used for treating attention deficit-hyperactivity disorder (ADHD), anxiety, chronic fatigue syndrome (CFS), Lyme disease, fibromyalgia, leg cramps during pregnancy, diabetes, kidney stones, migraine headaches, weak bones (osteoporosis), premenstrual syndrome (PMS), altitude sickness, urinary incontinence, restless leg syndrome, asthma, multiple sclerosis, and for preventing hearing loss.

Mechanism of Action

Acts as cofactor in numerous enzymatic reactions involving protein synthesis and carbohydrate metabolism; depresses CNS, produces anticonvulsant effects

Pharmacokinetics

Absorption/Bioavailability

Inversely proportional to amount ingested (15-36% at thigh doses and 40-60% at controlled dietary levels)

Distribution

50-60% (Bone); 1-2% (extracellular fluid).

Protein binding

30% (albumin)

Metabolism

Hepatic.

Excretion

Magnesium chloride is extensively metabolized. Less than 10% of the dose was excreted unchanged in the urine (as magnesium).

2. MATERIALS AND METHODS

2.1. Preparation of 0.1N HCl

8.5 ml of Concentrated HCl dissolved in 1000ml of distilled water to prepare a 0.1N HCl

2.2. Preparation of P^H 6.8 phosphate buffer

6.8gm of and 8 gm of sodium hydroxide dissolved in 1000 ml distilled water to prepare P^H 6.8 phosphate buffer.

2.3. Formulation Development

The pharmaceutical development studies have be carried out with the purpose of selecting right dosage form and stable formulation. These studies give detailed description of all the steps involved in the process development of Sustained release tablet. Such details are intended towards identifying critical parameters involved in the process, which have to be controlled in order to give reliable and reproducible quality product.

2.3.1. Formulation of sustained release tablet

The Sustained release tablet was prepared by Wet granulation method.

Preparation

- Drug(Magnesium Chloride) dissolved in purified water or Isopropyl alcohol(IPA).

- Dry mixing is done by mixing M.C.C.P-102 & HPMC K100M.
- Granulation can be done mixing by the mixture with purified water or IPA containing Drug.
- Above prepared granules will be kept for drying.
- Dry granules were passed through a #20 and mixed with HPMC K100M and Aerosil.
- Blend is mixed with magnesium stearate, talc.
- Compression

2.3.2. Trial formulations

Different formulation trial batches of Sustained release Magnesium chloride were formulated and studied for their release profiles to get the optimized formulation of Sustained release tablet.

2.3.3. Formulation trial batch of sustained release magnesium chloride tablet

The trial batch of Sustained release Magnesium chloride was prepared by employing drug with varying the percentage of polymer like HMPC K100M. Different percentages of polymer have been used in trial batch and studied to have Magnesium chloride sustaining effect for period of 8 hours (Table 1).

3. RESULTS AND DISCUSSION

3.1. Preparation of Absorption maxima for Magnesium Chloride using P^H6.8 Phosphate buffer

Accurately weighed amount of Magnesium chloride (890.17 mg) was dissolved in small quantity of P^H 6.8 Phosphate buffer and then diluted to 100 ml with the same solvent. From these solution 2 ml was taken and dissolved in 100 ml of P^H 6.8 Phosphate buffer. From these stock solution different standards of working standard solutions i.e., 1, 2, 3, 4, 5µg/ml were made up with P^H 6.8 Phosphate buffer and the absorbance was measured at 285.2 nm using P^H 6.8 Phosphate buffer as blank by Atomic absorption spectroscopic method. A graph was plotted by using concentration at X-axis and absorbance at Y-axis (Table 2 and Figure 1).

Table - 1: Formulation

Ingredients	Formulation Code (amount per tablet in mg)						
	F1	F2	F3	F4	F5	F6	F7
Magnesium Chloride	100	100	100	100	100	100	100
H.P.M.C K100M	-	-	22.500	22.500	22.5	45	67.5
M.C.C.P pH 102	200	177.5	177.5	155.00	271.25	248.75	226.25
Lactose	116.25	116.25	93.75	116.25	-	-	-
H.P.M.C K100M	22.50	45.000	45.000	45.000	45	45	45
Aerosil	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Talc	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Isopropyl alcohol *	300	300	300	300	300	300	300
Coating solution							
Instamoist WHITE	20	20	20	20	20	20	20
Isopropyl alcohol*	172.5	172.5	172.5	172.5	172.5	172.5	172.5
Methylene Chloride*	57.5	57.5	57.5	57.5	57.5	57.5	57.5
Total	470	470	470	470	470	470	470

Table - 2: Standard plot of Magnesium Chloride using P^H6.8 Phosphate buffer

Concentration µg/ml	Absorbance at 285.2nm
1	0.112
2	0.215
3	0.311
4	0.398
5	0.496

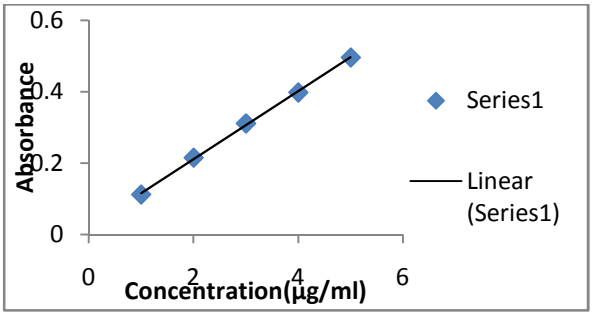

Figure - 1: Calibration Curve.

Table - 2: Dissolution studies of Magnesium Chloride using PH6.8 Phosphate buffer as media:

Time	F1	F2	3	F4	F5	F6	F7
2	60	50	55	58	55	47	32.6
4	85	65	76	73	73	65	50.6
6	99	99	99	99	99	88	75
8	99	99	99	99	99	99	98.7

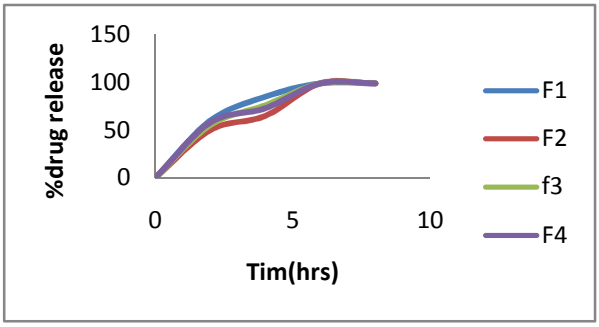

Figure -2: Drug release

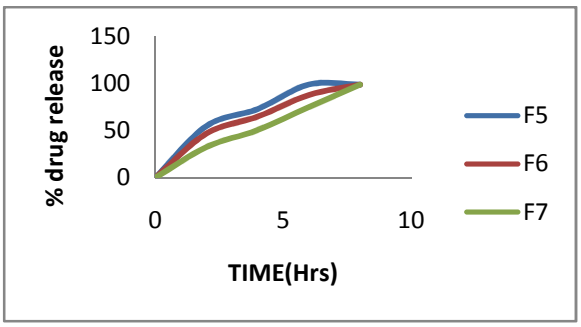

Figure -2(a): Drug release

Table - 3: Comparison of dissolution profiles of reference product and optimised product

Time	Reference product	Optimized product
2	39.4	32.6
4	61.9	50.6
6	86.1	75.1
8	97.6	98.7

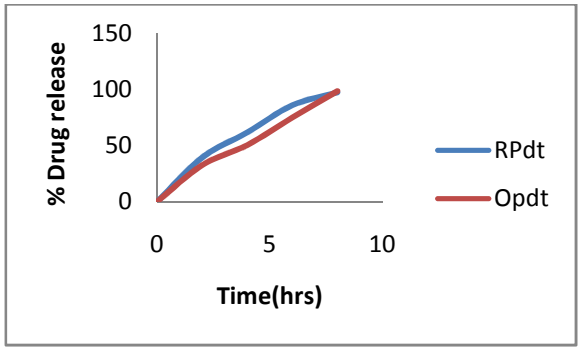

Figure – 3: Comparison of Drug release with reference product

3.2. Evaluation parameters

Trial batches of different formulations of individual tablets were prepared and evaluated for the following parameters.

Evaluation of granules

- Bulk Density
- Tapped Density
- Angle of Response
- Carr's Index
- Hausner's Ratio

Physical evaluation of tablet

- Weight variation
- Thickness
- Hardness
- Drug content analysis

In-vitro drug release study

- Tablet dissolution profile

3.3. Evaluation of Granules

3.3.1. Bulk density and tapped density

A measured quantity of granules was transferred to a measuring cylinder measuring its initial volume [V 0] and tapped mechanically either manually or using some tapping device till a constant volume [V f] and it includes the true volume of the granules and void space between them. The bulk density and tapped density was calculated by the following formulae. Bulk density is the ratio between a mass of granules and its bulk volume (v0). It is expressed by g/cc.

Bulk Density = Mass of Powder/
Bulk Volume of powder (V0)

Tapped density is the ratio between mass of granules and volume of the granules after tapping (Vf). It is expressed by gm/cc.

3.3.2. Compressibility Index and Hausner's Ratio

The Compressibility index and Hausner's ratio are measures the flow property of a powder to be compressed. As such, they measure the relative importance as inter particulate Interactions. In a free flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in values. For poorer flowing materials, Inter particulate interactions will be greater and greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner's ratio.

The compressibility index and Hausner's ratio are calculated by measuring the values for bulk density (ρ bulk) and Tapped Density (ρ tapped) as follows, and official limits are shown in the table

Compressibility index = Tapped density-bulk density/tapped density *100

Hausner's ratio is the measurement of fractional resistance of the drug and the ideal range should be 1.2-1.5 and the official limits are shown in the table

Hausner's Ratio= Tapped Density/Bulk Density

3.3.3. Physical evaluation of Tablet

Weight variation

Twenty tables were randomly selected from each batch and individually weighted. The average weight and standard deviation of 20 tablets were calculated. The batch passes the test for weight variation test if not more than two of the individual weight deviates from the average weight more than the percentage shown in the table no( ) and none should deviate by more than twice the percentage shown. The average weight and standard deviation of the tablets of each batch were given in the table.

Table – 4: Weight Variation (IP Limits)

Average weight of Tablet (mg)	Percentage Deviation
80 or less	10
80 to 250	7.5
More than 250	5

Hardness

The tablet-crushing load is the force required to break a tablet by compression. Hardness was measured by using hardness tester (Pfizer hardness tester). For each batch, six tablets were selected randomly and evaluated. Hardness of about 4-6 kg/cm^2 is considered to be minimum for uncoated tablets and for mechanical stability.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche Friabilator was used for the purpose. Reweighed sample of ten tablets were placed in the Friabilator, which was then operated for 100 revolutions. After 100 revolutions, the tablets were dusted and reweighted. Compressed tablets should not lose more than 1% of their weight.

Percentage Friability=Initial Weight -Final Weight/Final weight X 100

3.4. *In-vitro* Drug Dissolution Test

The *in-vitro* dissolution study was conducted in triplicate using USP Type-II dissolution apparatus. The study was carried out in 900 ml of phosphate buffer pH 6.8. The bath temperature was maintained at 37 ± 0.5°C. The paddle was rotated at 50 rpm. At different time intervals as described above, 10 ml sample was withdrawn and at each time of withdrawal, 10 ml of fresh corresponding medium was replaced into the dissolution flask. The samples were filtered through membrane filter and proper dilutions were made. The absorbance was measured at 285.2 nm against blank. The amount of drug was calculated using standard graph and the Using absorbance, percentage and cumulative percentage release were calculated.

3.5. Drug release kinetics

The dissolution data obtained was fitted to which kind of mathematical models like Zero order release kinetics, First order release kinetics, Higuchi equation, Hixson Crowell method and korsemeyer peppas equation to identify the rate and mechanism of release from the prepared formulations and marketed formulations. The correlation coefficients were calculated are used to find the fitness of the data.

Zero order release kinetics:

Time versus Cumulative % drug release.

First order release kinetics

Time versus log cumulative % drug remaining.

Higuchi's model

Square root time versus cumulative % drug released.

Korsmeyer-Peppa's model

Log time versus log cumulative % drug released.

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