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Research

Formulation And *In Vitro* Evaluation Of Dalfampridine Sustained Release Tablets By Using Various Polymers

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Abstract

In present investigation the sustained release tablets of Dalfampridine was formulated to study effect various natural polymers of Tragacanth, Acacia gum and Xanthan gum. The model is based on a novel dosage form designed to deliver a drug into the gastrointestinal tract in a controlled manner. Matrix tablets were prepared by direct compression method. As a pre-requisite and part of pre-formulation studies, drug along with selected excipients and as optimized formulation was subjected to FT-IR studies. It was found that no interaction among excipients occurred, as no extra peaks obtained. Tablets were evaluated for various IP-QC tests like hardness, friability, content uniformity and *in-vitro* drug release by USP paddle apparatus. It was found that the release of drug D3 formulation showed 99.83% the formulation was gave the better release than other formulations. In these nine formulations D3 formulation was showing highest release following Peppas release kinetics.

Keywords: Dalfampridine, Tragacanth, Acacia gum, Xanthan gum, direct compression and Sustained release matrix tablets.

INTRODUCTION

Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood levelof a drug often translates into better patient compliance, as well as enhanced clinical efficacyof the drug for its intended use.

The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ.

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

Rationale for extended release dosage forms[10-12]

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect.

Drawbacks of Conventional Dosage Forms[13]

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
3. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

Dissolution sustained systems

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the device until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

Reservoir Type

Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats as shown in figure, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals. Although this is not a true sustained release system, the biological effects can be similar. An alternative method is to administer the drug as group of beads that have coating of different thickness. This is shown in figure. Since the beads have different coating thickness, their release occurs in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating. This is the principle of the spansule capsule. Cellulose nitrate phthalate was synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.

Matrix Type

The more common type of dissolution sustained dosage form (as shown in figure 4). It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion

Two types of dissolution sustained pulsed delivery systems

- ✓ Single bead type device with alternating drug and rate-controlling layer.
- ✓ Beads containing drug with differing thickness of dissolving coats.

Amongst sustained release formulations, hydrophilic matrix technology is the most widely used drug delivery system due to following advantages

- ✓ Provide desired release profiles for a wide therapeutic drug category, dose and solubility.
- ✓ Simple and cost effective manufacturing using existing tableting unit operation equipment
- ✓ Robust formulation.
- ✓ Broad regulatory and patient acceptance.
- ✓ Ease of drug release modulation through level and choice of polymeric systems and function coatings.

Methods Using Ion Exchange

It is based on the formation of drug resin complex formed when anionic solution is kept in contact with ionic resins. The drug from these complexes gets exchanged in gastro intestinal tract and released with excess of Na+ and Cl- present in gastrointestinal tract.

Anion Exchangers: Resin+ - Drug- + Cl- goes to Resin+- Cl-+ Drug-

Cation Exchangers: Resin-- Drug+ + Na+ goes to Resin- - Na+ + Drug+

These systems generally utilize resin compounds of water insoluble cross linked polymer. They contain salt forming functional group in repeating positions on the polymer chain. The rate of drug diffusion out of the resin is sustained by the area of diffusion, diffusional path length and rigidity of therein which is function of the amount of cross linking agent used to prepare resins. The release rate can be further sustained by coating the drug resin complex by microencapsulation process.

Methods Using Osmotic Pressure

A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

Two types of osmotically sustained systems are

- ✓ Type A contains an osmotic core with drug.
- ✓ Type B contains the drug in flexible bag with osmotic core surrounding.

pH– Independent Formulations

The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release e.g. propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility.

Altered Density Formulations

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug content is released, it would have limited utility. To this end, several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

High Density Approach:

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4gm/cm3.

Low Density Approach:

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.

Matrix tablets[9]

One of the least complicated approaches to the manufacture of controlled release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. Examples of Retardant.

Classification of matrix tablets[20,21]

On the basis of polymer used

Hydrophilic matrix tablet

Hydrophilic matrix can be utilized as a means to control the drug release rate. The matrix may be tabulated by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion in drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The effect of formulation and processing variables on drug release behaviour from compressed hydrophilic matrices has been studied by number of investigators. The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follow,

Cellulose derivatives

- ✓ Hydroxyethylcellulose,
- ✓ Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cps,
- ✓ Sodium carboxy methyl cellulose and
- ✓ Methyl cellulose 400 and 4000 cps.

Non-cellulose natural or semi synthetic polymers

- ✓ Agar-agar, Carob Gum, Alginates,
- ✓ Molasses, Polysaccharides of mannose and
- ✓ Galactose, Chitosan and Modified starches.

Polymers of acrylic acid

- ✓ Polymer which is used in acrylic acid category is Carbopol 934.

Other hydrophilic materials

- ✓ Alginic acid,
- ✓ Gelatin and
- ✓ Natural gums.

Fat-wax matrix tablet

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminute for controlled-release granulations. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders. The drug embedded into a melt of fats and waxes is released by leaching and/ or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the GIT. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix.

Plastic matrix tablet (hydrophobic matrices)

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. Controlled release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be comminute or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by.

- The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.
- The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.
- Using latex or pseudo latex as granulating fluid to granulate the drug and plastic masses. For example: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.

Bio-degradable matrices

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. It is biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process into olegomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly (esters) and poly anhydrides. v) Mineral matrices: These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

MATERIALS

Dalfampridine-Procured FromAktteva Biopharma LLP, Gujarat. Provided by SURA LABS, Dilsukhnagar, Hyderabad, Tragacanth-Loba ChemiePvt. Ltd Mumbai, India, Acacia gum-Merck Specialities Pvt Ltd, Mumbai, India, Xanthan gum-Aravind Remedies (AR), Chennai, India, PVP-K 30-Unify chemicals, Jothi Aromas andDK Enterprises, India, Aerosil -S.D. Fine Chemicals. India, Magnesium Stearate-Merck Specialities Pvt Ltd, Mumbai, India, MCC-S.D. Fine Chemicals, India.

METHODOLOGY

Analytical method development

Determination of λ max

100mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 100 ml volumetric flask and made it up to 100ml with the media (Secondary stock solution–100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of calibration curve

100mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 10 ml was pipette out into 100 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by thequality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Indian Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat

horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\mathbf{Tan\ \theta = h / r}$$

Tan θ = Angle of repose
h = Height of the cone,
r = Radius of the cone base

Table 1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as themass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.
The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where,M = weight of sample
V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk densitythe cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$Tap = M / V$$

Where,Tap= Tapped Density
M = Weight of sample
V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

Table 2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of Tablets

All the formulations were compress by direct compression. The compositions of different formulations are given in Table 7.4.The tablets were prepared as per the procedure given below and aim is to prolong the release of Dalfampridine. Total weight of the tablet was considered as 120mg.

Procedure

1) Dalfampridine and all other ingredients were individually passed through sieve no ≠ 60.

2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 3: Ingredients and Uses

Ingredients	Uses
Dalfampridine	API
Tragacanth	Binding Agent
Acacia Gum	Binding Agent
Xanthan Gum	Binding Agent
PVP K 30	Binding Agent
MCC	Diluent
Magnesium stearate	Lubricant
Aerosil	Anticaking agent

Table 4: Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION								
	D1	D2	D3	D4	D5	D6	D7	D8	D9
Dalfampridine	10	10	10	10	10	10	10	10	10
Tragacanth	10	20	30	-	-	-	-	-	-
Acacia gum	-	-	-	10	20	30	-	-	-
Xanthan gum	-	-	-	-	-	-	10	20	30
PVP-K 30	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4
MCC									
Total Weight	120	120	120	120	120	120	120	120	120

RESULTS AND DISCUSSION

The present study was aimed to developing sustained release tablets of Dalfampridine using various polymers. All the formulations were evaluated for physicochemical propertiesand *in vitro* drug release study.

Analytical method

Graphs of Dalfampridine were taken in 0.1N HCLand in pH 6.8 phosphate buffer at 247 nm and 250 nm respectively.

Table 5: Observations for graph of Dalfampridine in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
10	0.138
20	0.266
30	0.397
40	0.511
50	0.635

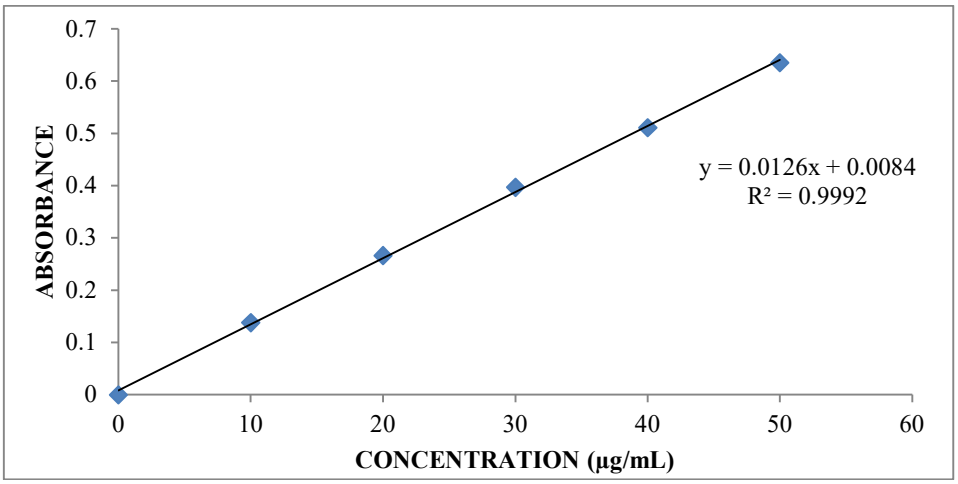

Fig 1: Standard curve of Dalfampridine

Table 6: Standard graph values of Dalfampridine at 250nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
10	0.205
20	0.397
30	0.561
40	0.768
50	0.935

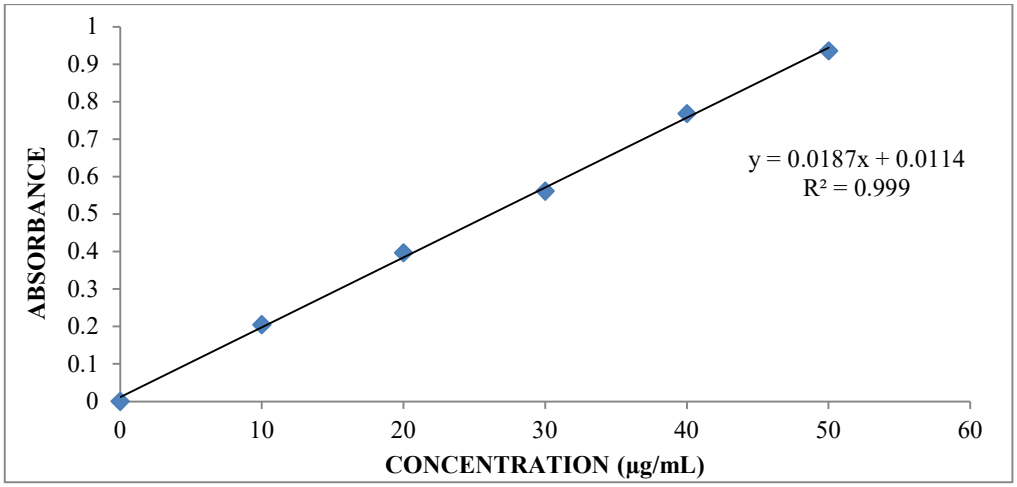

Fig 2: Standard curve of Dalfampridine

Preformulation parameters of powder blend

Table 7: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
D1	24.72 ± 0.01	0.345 ± 0.018	0.401 ± 0.012	13.97 ± 0.01	1.16 ± 0.02
D2	19.66 ± 0.02	0.332 ± 0.002	0.375 ± 0.015	11.46 ± 0.01	1.13 ± 0.01
D3	20.16 ± 0.015	0.465 ± 0.015	0.532 ± 0.001	12.59 ± 0.01	1.14 ± 0.01

D4	21.41 ± 0.01	0.421 ± 0.002	0.492 ± 0.002	14.43 ± 0.02	1.17 ± 0.02
D5	20.60 ± 0.015	0.382 ± 0.001	0.439 ± 0.002	12.98 ± 0.01	1.15 ± 0.01
D6	20.36 ± 0.015	0.523 ± 0.002	0.604 ± 0.017	13.41 ± 0.02	1.15 ± 0.01
D7	19.98 ± 0.01	0.348 ±0.001	0.401 ± 0.001	13.22 ± 0.01	1.15 ± 0.01
D8	40.13 ± 0.01	0.412 ±0.015	0.530 ±0.021	22.23 ± 0.01	1.29 ± 0.01
D9	39.90 ± 0.01	0.424 ± 0.001	0.517 ± 0.01	18.00 ± 0.01	1.21 ± 0.01

All the values represent n=3

Tablet powder blend was subjectedto various preformulationparameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties.The tapped density of all the formulations powders has good flow properties.The compressibility index of all the formulations was found to be 11.46 to 22.23 which show that the powder has good flow properties.All the formulations has shown the hausner ratio 1.13 to 1.29 indicating the powder has good flow properties.

Quality control parameters for tablets

Tablet quality control tests such as weight variation, hardness, friability, thickness and drug release studies in different media were performed on the compression tablet.

Table 8: Quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
D1	119.69	5.8	0.58	3.18	96.52
D2	120.04	5.1	0.34	3.99	99.60
D3	118.76	5.7	0.25	3.82	98.14
D4	116.25	5.0	0.49	3.71	97.50
D5	119.03	5.4	0.66	3.90	99.13
D6	117.42	5.9	0.72	3.65	98.36
D7	119.78	5.6	0.31	3.59	96.42
D8	118.45	5.4	0.26	3.98	99.14
D9	118.14	5.2	0.44	3.85	98.73

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 116.25to 120.04mg, so the permissible limit is ±7.5% (>120 mg). The results of the test showed that, the tablet weights were within the limit.

Hardness test

Hardness of the five tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 5.0 to 5.9 kg/cm^2,which was within IP limits.

Thickness

Thickness of five tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 3.18to 3.99 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table-8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 96.42 - 99.60 %.
All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In vitro* drug release studies**

Table 9: Dissolution data of Dalfampridine tablets D1-D9

Time (H)	% OF DRUG RELEASE								
	D1	D2	D3	D4	D5	D6	D7	D8	D9
0	0	0	0	0	0	0	0	0	0
0.5	16.93	21.60	10.49	19.36	15.82	12.93	06.19	10.28	12.39
1	28.56	27.08	16.16	27.83	22.91	18.58	10.82	15.34	19.55
2	39.71	33.14	25.58	33.91	28.37	23.32	18.75	20.64	25.02
3	45.82	40.95	32.14	40.76	34.59	28.96	23.90	26.12	30.34
4	56.63	46.39	40.99	45.29	41.76	31.84	29.16	33.86	37.19
5	62.50	52.14	48.75	52.78	47.23	36.12	35.35	42.92	42.88
6	66.97	60.82	55.68	57.12	55.99	42.59	40.71	46.14	50.92
7	78.65	65.79	62.83	66.89	61.87	48.76	46.45	53.08	56.17
8	84.96	73.62	67.94	70.34	67.50	54.88	53.59	60.36	64.93
9	96.53	80.26	73.58	79.29	72.14	58.09	61.73	67.76	71.87
10		92.81	81.06	84.86	76.99	63.23	78.96	75.33	77.15
11		97.36	92.23	87.53	81.12	69.24	81.11	87.98	85.99
12			99.83	93.14	87.39	75.16	88.95	91.46	95.38

Different formulations (D1-D9) were prepared using different polymers like Tragacanth, Acacia gum and Xanthan gum alone at different ratios. Formulations D1-D3 were prepared using Tragacanth at the ratio of 1:1, 1:2 and 1:3 which showed the drug release about 96.53% at 9h, 97.36% 11h and 99.83 at 12h %. Formulations D4-D6 were prepared using Acacia gum at the ratio of 1:1, 1:2 and 1:3 with the drug release of 93.14%, 87.39and 75.16% and the formulations D7-D9 were prepared by using Xanthan gum polymer at the ratio of 1:1, 1:2 and 1:3 Showed the drug release of 88.95%, 91.46% and 95.38% at the end of 12 h. Among all these formulations D3 was selected as the best ideal formulation which exhibited 99.83% of drug release in 12 h. Finally Concluded that D3 formulation was considered as optimized formulation.

Table 10: Release kinetics

Cumulative (%) Release Q	Time (T)	Root (T)	Log(%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release / T)	1/Cum% Release	Peppas Log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
10.49	0.5	0.707	1.021	-0.301	1.952	20.980	0.0953	-0.979	89.51	4.642	4.473	0.168
16.16	1	1.000	1.208	0.000	1.923	16.160	0.0619	-0.792	83.84	4.642	4.377	0.265
25.58	2	1.414	1.408	0.301	1.872	12.790	0.0391	-0.592	74.42	4.642	4.206	0.435
32.14	3	1.732	1.507	0.477	1.832	10.713	0.0311	-0.493	67.86	4.642	4.079	0.563
40.99	4	2.000	1.613	0.602	1.771	10.248	0.0244	-0.387	59.01	4.642	3.893	0.748
48.75	5	2.236	1.688	0.699	1.710	9.750	0.0205	-0.312	51.25	4.642	3.714	0.927
55.68	6	2.449	1.746	0.778	1.647	9.280	0.0180	-0.254	44.32	4.642	3.539	1.103
62.83	7	2.646	1.798	0.845	1.570	8.976	0.0159	-0.202	37.17	4.642	3.337	1.304
67.94	8	2.828	1.832	0.903	1.506	8.493	0.0147	-0.168	32.06	4.642	3.177	1.465
73.58	9	3.000	1.867	0.954	1.422	8.176	0.0136	-0.133	26.42	4.642	2.978	1.663
81.06	10	3.162	1.909	1.000	1.277	8.106	0.0123	-0.091	18.94	4.642	2.666	1.976
92.23	11	3.317	1.965	1.041	0.890	8.385	0.0108	-0.035	7.77	4.642	1.981	2.661
99.83	12	3.464	1.999	1.079	-0.770	8.319	0.0100	-0.001	0.17	4.642	0.554	4.088

Table 11: Kinetics Correlation coefficient values

Release kinetics	Correlation coefficient values
Zero order release kinetics	$R^2 = 0.988$
Higuchi release kinetics	$R^2 = 0.969$
Peppas release kinetics	$R^2 = 0.996$
First order release kinetics	$R^2 = 0.896$

From the above graphs it was evident that the formulation D3 was followed Peppas release mechanism.

Drug – Excipient compatibility studies

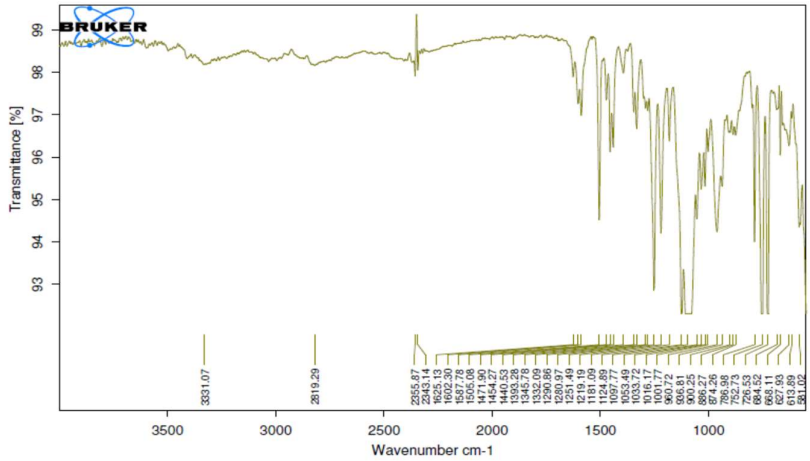

Fig 3: FT-TR Spectrum of Dalfampridine pure drug

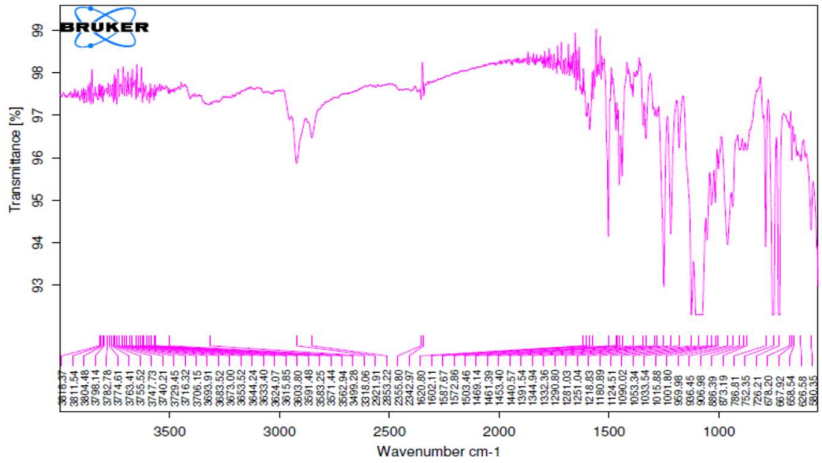

Fig 4: FT-IR Spectrum of Optimised Formulation

From the above studies it was found that there was no shifting in the majorpeaks which indicated that there were no significant interactions occurred between the Dalfampridine and excipients used in the preparation of different DalfampridineSustained release formulations. Therefore the drug and excipients are compatible to form stable.

Formulations under study. The FTIR spectra of Dalfampridine and physical mixtureused for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

CONCLUSION

Dalfampridine is a potassium channeldrug with multiple sclerosiswhich is used for thebetter treatment of multiple sclerosis. The present investigation was concerned with the development ofthe sustained release matrix tablets, which after oraladministration were designed to prolong theduration of action. Various formulations weredeveloped by using release rate controlling and gelforming polymers like Tragacanth, Acacia gum and Xanthan gumin single by direct compression method. The active pharmaceutical ingredient Dalfampridine was evaluated for itsphysical characteristics, analytical profiles and drug polymer compatibility study. Thegranules were prepared by direct compression method. The prepared granules wereevaluated for Angle of repose, Bulk density, Tapped density and Carr's index. Theresults obtained were found to be satisfactory and within the specified limits. After compression parameters like Thickness, Hardness, Weight variation, Friability, content uniformity and *In-vitro* release studies were evaluated. Result of the present study demonstrated that natural polymers could besuccessfully employed for formulating sustained release matrix tablets of Dalfampridine. In present studies, D3 formulation containing Tragacanth 30mg is probably showing release up to 99.83% within 12 hrs. According to drug release study it was found that there D3 formulation was showed maximum % of drug release in desired period of time and it is considered as optimised formulation (D3).

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