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MODIFIED RELEASE FORMULATION DRUG DELIVERY SYSTEM FOR CARDIOVASCUALR DRUGS

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Abstract

The objective of this research work is mainly to develop a concept for modified release formulation using acid bead solubliser as a core and utilise this concept todeliver actives of cardiovascular category such as Dipyridamole and CarvedilolPhosphate from a bead/ Pellet formulation. Aspirin is used in combination withdipyridamole to produce synergistic effect to reduce clot formation, in this researchwork a novel aspirin pellet formulation is developed which can be used incombination with any other actives to provide synergistic effect. The major focus ofthis platform technology development is to come up with possible generic costeffective pharmaceutically equivalent formulation. Attempt has been made to investigate Dipyridamole as model drug and under similar concept Carvedilolphosphate was investigated using acid bead technology. A pH modulation iscommonly used to develop a product with actives which has pH dependant solubility.Dipyridamole and Carvedilol phosphate fall under same category of cardiovascular drugs with pH dependant solubility; hence this proposed platform can be evaluated forboth the drugs. Both products do not have generic formulation in the US market; thisprovides a great challenge to overcome product limitations to have stable,bioequivalent, commercially viable product. Dipyridamole modified release capsule isavailable as Aggrenox® in USA, Persantin® in UK & Asasantin® in UK, Australia.

Key words: Carvedilol Phosphate, Dipyridamole, cardiovascular drugs, Modified release, Pellet.

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INTRODUCTION

Oral route of drug administration is the most important and widely used method ofadministering drugs for systemic effects; these requirements provide a need for controlled-release technologies that can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required. The ever increasing cost of bringing new drugentities to market has been instrumental in generating interest in platform controlled- release drug delivery systems (CRDDS). Dipyridamole and Carvedilol Phosphate are drugs belonging to the class of cardiovascular drugs used in treatment of various disease conditions. For an effective therapy for these chronic indications, drugs have to be delivered at a constant or modified rate with minimal fluctuations in the plasma concentration for longer duration. Various technologies can be developed to achieve this; focus of this research work is to develop a platform drug delivery technology for delivery of drugs having pH dependant solubility. An attempt of developing a novel formulation drug delivery technique shall be done by using Dipyridamole as a model drug from cardiovascular category and the application of this technology with suitable modifications shall be tested for Carvedilol phosphate to confirm the delivery mechanism for the formulation. The market for oral controlled drug delivery alone is expected to grow at 9% or more every year .

MATERIALSANDMETHODS

Dipyrimidamole (TH; M/s Mylan Laboratories Pvt. LTD. India), API & impurities were obtained from VerGo Pharma Research Laboratories,Goa,India.Di sodium hydrogen phosphates [AR Grade], Acetonitrile [HPLC Grade], Orthophosphoric acid were from Merck . Water was purified by Millipore. Milli-Q water purification system and was passed through a 0.22 μm membrane filter before use.

Clinical The reference listed drug AGGRENOX® (aspirin, extended-release dipyridamole) is a combination antiplatelet agent intended for oral administration. Each hard gelatine capsule contains 200 mg dipyridamole in an extended-release form and 25 mg aspirin, as an immediate-release sugar-coated tablet.

Mechanism of Action The antithrombotic action of Aggrenox® (aspirin/extended-release dipyridamole) capsules is the result of the additive antiplatelet effects of dipyridamole and aspirin.

Dipyridamole: Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes in vitro and in vivo; the inhibition occurs in a dose-dependent manner at therapeutic concentrations (0.5–1.9 g/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A2-receptor thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3',5'-adenosine monophosphate (cAMP) levels.

SEM ANALYSIS: To understand the surface morphology of the reference product, Innovator pellets were exposed to SEM analysis. SEM investigation generally provides insight on the formulation design, surface and inner surface morphology. The objective of this investigation was to get more clarity on reference product. SEM Analysis: Reference Product SEM analysis was carried out to understand morphology of product and get insight on product design.

DRUG RELEASE PROFILE OF INNOVATOR PRODUCT Dissolution of Reference Product in OGD media: The drug release of the AGGRENOX® (aspirin, extended-release dipyridamole) was characterized as per OGD dissolution

method using USP apparatus I at 100 rpm in 900 mL in 0.01 N HCl for first hour, followed by 0.1 M Phosphate Buffer, pH 5.5, for 7 Hr

2 PHYSICAL EVALUATION: TAppearance Intensely yellow crystalline powder Particle Size D 90 less than 20 microns Identification By IR : Spectrum should match with the working standard's spectrum By HPLC: The retention time of the major peak in the chromatogram of the related substances preparation corresponds to that in

DIFFERENTIAL SCANNING CALORIMETRY: DSC study was carried out to understand the melting endotherm for API.

POLYMORPHISM [XRD STUDY]: XRD study was carried out to understand crystalline nature of the API and existence of any polymorphic form

SOLUBILITY: Dipyridamole is practically insoluble in water and shows pH dependent solubility, hence to understand the same in detail, BCS solubility experimentation was carried out.

HYGROSCOPICITY STUDY: It is found that Dipyridamole is non-hygroscopic according to literature. (Source: DMF data and supplier information)

FORMULATION DEVELOPMENT: PHASE I: DIPYRIDAMOLE ER PELLETS DEVELOPMENT The aim of formulation development was to formulate Aspirin/Extended release dipyridamole capsule which are stable, reproducible, scalable, & bioequivalent to the reference product Aggrenox®. The prototype formula composition of the product was arrived after taking numerous development trials and the qualitative and quantitative formula composition was arrived upon based on identified risks & CQAs. The formulation development work was initiated with the commonly used excipients for pellets formulation

SOLUTION SUSPENSION PREPERATION METHOD A general procedure was followed to achieve either drug suspension or polymeric coating solution. In a clean SS container an exact weighed amount of solvent is taken in which drug or polymers are dispersed in the same under constant stirring to form a uniform drug or polymeric dispersion or solution. The solution or dispersion is filtered through # 80 mesh and used for coating the particles under continuous stirring

SELECTION OF FORMUALTION DESIGN: The proposed technology design hypothesis is based on use of polymeric coating which can control the release of Tartaric acid in such a way that it will ensure simultaneous release of dipyridamole. The modified release coated tartaric acid pellets design is proposed based on use of hydrophilic and hydrophobic or combination of both polymers to achieve desired drug release profile. The use of these polymers either in seal coat I and or seal coat II have direct impact on the formulation performance. Initially to shortlist seal coat I design was targeted as enumerated below. In this design Seal coat II design was kept constant as per proposed hypothesis.

RESULTS AND DISCUSSION

ANALYTICAL METHODS – DIPYRIDAMOLE

Preparation of Buffer: Dissolve 1.0 g of Disodium hydrogen phosphate anhydrous in 1000 ml of Milli-Q water and adjust the pH to 2.50 with 10% Orthophosphoric acid. Filter through 0.45 µm membrane filter

Preparation of Mobile phase/diluent: Mix 680 ml of buffer with 320 ml of Acetonitrile, sonicate and degas for 10 min**.**

Preparation of Dipyridamole Standard stock solution: Accurately weigh and transfer 200 mg of Dipyridamole Working

Standard into a 100 ml volumetric flask add about 50mL of diluent and sonicate it to dissolve, make up with diluent and mix well

DISSOLUTION: DIPYRIDAMOLE

0.01N Hydrochloric acid: Dilute 8.5 ml of concentrated Hydrochloric acid to 1000 mL with Elix water. in a volumetric flask. Dilute 100 ml of above solution to 1000 ml with purified water in a volumetric flask

Dissolution Parameters: Table No. 134 Medium : 0.01 N Hydrochloric acid followed by 0.1 M , pH 5.5 Phosphate buffer Quantity : 900 ml Apparatus : Apparatus I (Basket) RPM : 100 Temperature : 37 ± 0.5 °C Time : 30 & 60 minutes in 0.1 N Hydrochloric acid 1, 2, 5, 7, 9 & 13 hr in 0.1 M , pH 5.5 Phosphate buffer

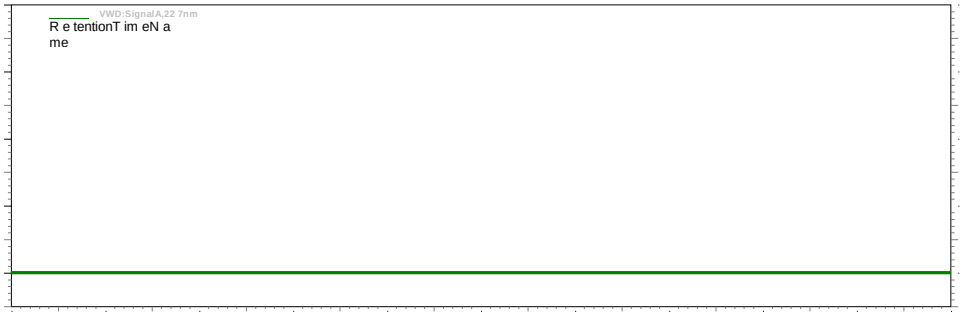
ANALYTICAL METHODS FOR CARVEDILOL PHOSPHATE

Preparation of Buffer: Weigh accurately and dissolve 1.36 g of Potassium dihydrogen phosphate in 1000 ml of MilliQ water and add 2 ml of Trifluoroacetic acid. Adjust the pH to 2.5 with diluted Potassium hydroxide solution. Note: Filter through 0.45µm Nylon 66 membrane filter

SPECIMEN CHROMATOGRAM OF ASPIRIN AND DIPYRIDAMOLE EXTENDED RELEASE CAPSULES 25MG/200MG [DISSOLUTION]

A) Dissolution:Aspirin

Dissolution:Blank

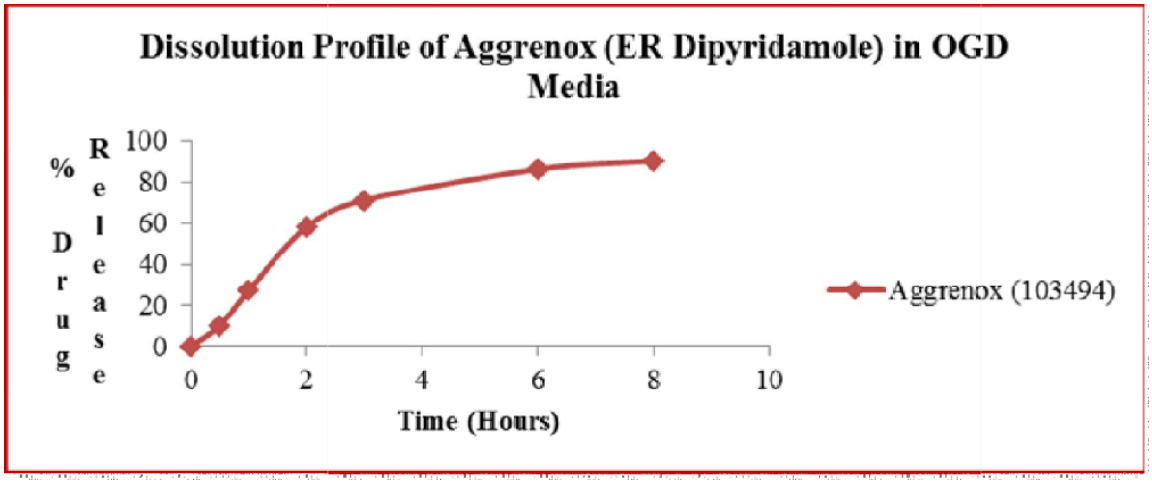


DISSOLUTION PROFILE OF TARTARIC ACID AND CARVEDILOLPHOSPHATE:

Column	**:**	Confidential
Flowrate	**:**	1.0mL/min.
Detection program:	**:**	210nm
Injectionvolume	**:**	10µL
Columntemperature	**:**	30ºC
Runtime	**:**	15minutes

Time(min)	**A%**	**B%**
0	100.0	0.0

ReferenceProduct:Aggrenox(Dipyridamole)								BatchNo:103494			
Apparatus:USPI		Volume:900ml						RPM:100			
Media	**Time (Hour)**	**%DipyridamoleRelease**						**AVG**	**Min**	**Max**	**% RSD**
		1	**2**	**3**	**4**	**5**	**6**				
0.01NHCL	0	0	0	0	0	0	0	0	0	0	0
	0.5	10	10	9	9	9	10	**10**	9	10	5.8
	1	27	28	27	26	27	28	**27**	26	28	2.8
pH 5.5 Phosphate Buffer	2	57	60	58	57	58	59	**58**	57	60	2.0
	3	70	73	71	70	71	71	**71**	70	73	1.5
	6	87	89	86	85	87	86	**87**	85	89	1.6
	8	90	93	91	88	90	90	**90**	88	93	1.8



FORMULATION DEVELOPMENT:PHASEI: DIPYRIDAMOLE ERPELLETS DEVELOPMENT

Batch Number	#32C&6100
Method	SBOA
Dissomedium	**0.01NHCl**forfirsthour,0.1MPhosphateBuffer,pH5.5, Thereafter
Volume	900mleach
Apparatus	USPIBasket
Speed	100
TimePoints	Acid:10,20,30,45,and60min;Buffer:1,2,5,and7hrs.

TARTARIC ACID PELLETS SIZE SELECTION:

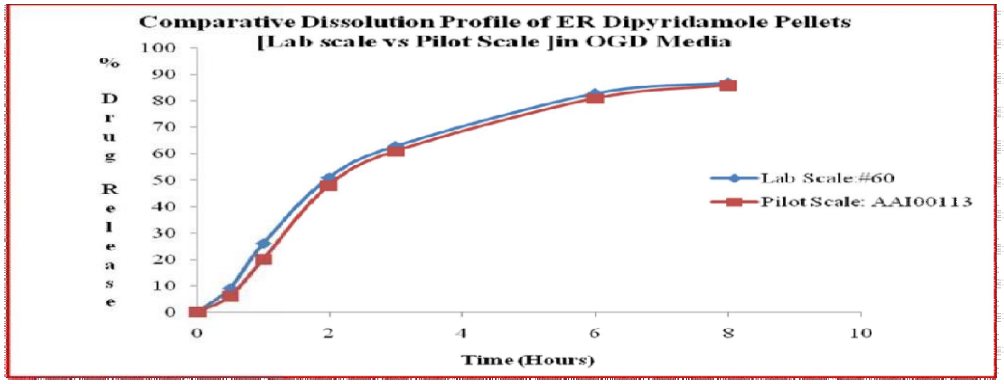
BatchNo.:006[TAP-400]								
Apparatus:USP I	**Volume:900ml**				**RPM:100**			
Media	**TimePts. (hr.)**	**%DrugRelease**			**Avg.**	**Min.**	**Max.**	**% RSD**
		Cap1	Cap2	Cap3				
0.01NHCl	0.5	11	10	11	11	10	11	5.413
	1	26	25	26	26	25	26	2.249
pH 5.5 PO4 Buffer	2	49	48	49	49	48	49	1.186
	3	61	59	61	60	59	61	1.914
	6	84	82	85	84	82	85	1.826
	8	88	88	90	89	88	90	1.302

SELECTION OF FORMULATION DESIGN:

BatchNo.:016D1								
Apparatus:USPI	**Volume:900ml**				**RPM:100**			
Media	**Time Pts. (hr.)**	**%DipyridamoleRelease**			**Avg.**	**Min.**	**Max.**	**% RSD**
		Cap1	Cap2	Cap3				
0.1NHCl	0.5	9	9	9	9	9	9	0.000
	1	23	24	24	24	23	24	2.440
pH5.5PO4 Buffer	2	45	46	46	46	45	46	1.264
	3	55	56	56	56	55	56	1.037
	6	63	64	63	63	63	64	0.912
	8	64	65	64	64	64	65	0.897

COMPARATIVE DISSOLUTION PROFILE OF DIPYRIDAMOLE ER COATED PELLETS MANUFACTURED AT LAB SCALE & PILOT SCALEIN OGD MEDIA

TestProduct:Lab scale				BatchNo.:060				
Apparatus:USPI	Volume:900ml			RPM:100				
Media	TimePts.	%DrugRelease			Avg.	Min.	Max.	%
	(hr.)	Cap1	Cap2	Cap3				RSD
0.01NHCl	0.5	9	9	9	9	9	9	0.000
	1	26	26	26	26	26	26	0.000
pH5.5PO4 Buffer	2	51	52	51	51	51	52	1.125
	3	63	64	63	63	63	64	0.912
	6	82	83	83	83	82	83	0.698
	8	87	86	87	87	86	87	0.666



CONCLUSIONS

This platform technology is being successfully applied to basic drugs which are soluble in presence of acid. In future detail in-vivo investigation of multiple drugs can be done to check impact of acidic solubliser in thesystem. This technology can be applied to achieve in situ solubilisation ofactive within the formulation, which then allows the solublised active to bediffusedoutfromthesystem...

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