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Research Article

Formulation and *in vitro* evaluation of glucosamine hydrochloride modified release tablets

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ABSTRACT

The present study was aimed towards the formulation and evaluation of Glucosamine Hydrochloride modified release tablets of 1500mg tablets in aiming to control the release over 24hours with bi-phasic release model as immediate release followed by controlled release of the dosage form. Around 40% of Glucosamine Hydrochloride i.e., 600mg was aimed to release immediately and remaining 60% of Glucosamine Hydrochloride was aimed to release in a controlled manner. Different grades at different concentrations of hydroxy propyl methylcellulose were used to achieve controlled release. Blend parameters, Physical parameters and Dissolution profile were taken as the basis to optimize the controlled release tablet. It was observed that formulation F7 was able to control the release of Glucosamine till 24hrs.

Keywords: Accelerated stability; Bi-Phasic release; Glucosamine hydrochloride; HPMC K100M; HPMC K200M; *In-vitro* dissolution; Modified release

INTRODUCTION

Glucosamine is a naturally occurring substance in the body found primarily in cartilage and plays an important role in maintaining cartilage health and function. The production of Glucosamine from glucose and glutamine is the rate limiting step in glycosaminoglycan synthesis and therefore the building and rebuilding of cartilage (Reginster et al., 2007).

Glucosamine is needed to make glycosaminoglycans (GAGs), which are proteins that make up the "ground substance" of cartilage. These proteins bind water in the cartilage matrix. These glycosaminoglycans form the tissue that binds collagen. Together, collagen and glycosaminoglycans maintain and rebuild cartilage. Glucosamine from either glucosamine hydrochloride or glucosamine sulfate has been shown to regenerate cartilage and exhibit some anti-inflammatory effects. (Ranganath Muniyappa et al., 2006). Glucosamine must be synthesized by the body, but the ability to do this declines with age. Glucosamine and its salts have therefore been advocated in the treatment of rheumatic disorders including osteoarthritis. The elimination half-life is around 3 hours; hence it requires repeated dosing as an immediate release tablet form. Current marketed formulations are available as immediate release dosage form of 500mg to be administered 3 times a day.

In the present study, Glucosamine Hydrochloride modified release tablets of 1500mg were prepared in aiming to control the release over 24hours with bi-phasic release model as immediate release followed by controlled release of the dosage form. Around 40% of Glucosamine Hydrochloride i.e., 600mg was aimed to release immediately and remaining 60% Glucosamine Hydrochloride was aimed to release in a controlled manner. Glucosamine is generally used in the form of either sulfate salt (potassium/sodium) or hydrochloride salt orally for the treatment of Osteoarthritis or degenerative joint diseases.

MATERIALS AND METHODS

MATERIALS

Glucosamine Hydrochloride was obtained from Exotic naturals, Mumbai. HPMC K100M and HPMC K200M were obtained from Zhejiang haishen chem. co ltd, China. Calcium hydrogen phosphate anhydrous was obtained from Shijiazhuang unison co ltd, China. Povidone K 90F was obtained from BASF, Mumbai. Stearic acid was obtained from Synpro, Mumbai. Microcrystalline cellulose PH 102 was obtained from Yashica Pharmaceuticals, Mumbai. Colloidal silicon dioxide was obtained from Bee chem., Kanpur, Uttar Pradesh.

METHODS

Preparation of Modified release Tablets

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Table 1: Composition of all batches F1-F7

Composition	Unit formula (mg/tablet)						
	F1	F2	F3	F4	F5	F6	F7
Intra granular portion							
Glucosamine HCl	900	900	900	900	900	900	900
HPMC K100M	90	180	360	---	---	---	---
HPMC K200M	---	---	---	45	90	135	180
Calcium hydrogen phosphate anhydrous	60	60	60	60	60	60	60
Binder solution							
Povidone K90F	40	40	40	40	40	40	40
water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Extra granular portion							
Glucosamine HCl	600	600	600	600	600	600	600
MCC PH 102	60	60	60	60	60	60	60
Stearic acid	18	18	18	18	18	18	18
Colloidal silicon dioxide	18	18	18	18	18	18	18
Total tablet weight	**1786**	**1876**	**2056**	**1741**	**1786**	**1831**	**1876**

Table 2: Evaluation of lubricated blend and compressed tablets

Batch No	Blend Parameters				Physical Parameters of Tablets		
	Loss on drying (%)	Bulk density (gm/cc)	Tapped density (gm/cc)	Comp. Index (%)	Hardness (N)	Friability (%)	Average weight (mg)
F1	1.2	0.72	0.83	13	24 ± 0.8	0.27	1787.2 ± 1.52
F2	1.0	0.75	0.88	15	26 ± 0.5	0.33	1876.9 ± 3.41
F3	1.2	0.72	0.85	15	23 ± 0.9	0.25	2057.3 ± 2.98
F4	1.5	0.71	0.78	09	25 ± 0.5	0.14	1740.5 ± 4.23
F5	1.6	0.70	0.80	13	23 ± 0.4	0.18	1786.4 ± 4.54
F6	1.5	0.72	0.82	12	19 ± 0.5	0.21	1832.7 ± 4.26
F7	1.4	0.74	0.81	09	20 ± 0.4	0.19	1875.2 ± 3.25

Glucosamine HCl modified release tablets were prepared by wet granulation technique using two different polymers such as HPMC K100M, HPMC K200M as a rate controlling polymers. The batches F1-F3 were prepared with HPMC K100M alone in various concentrations and the batches F4-F7 were prepared with HPMC K200M alone in various concentrations. The process of tablet preparation is same for all batches except polymer change. (Raymond C Rowe, 2009)

Glucosamine hydrochloride was divided in two portions, 900mg as intra granular portion and 600mg as extra granular portion. Then sifted and collected separately Glucosamine hydrochloride, HPCM K100M, HPMC K200M, Calcium hydrogen phosphate anhydrous, Povidone K90 F, MCC PH 102, Stearic acid and Colloidal silicon dioxide through #40mesh in a poly ethylene bag. The Binder solution was prepared by dissolving Povidone K90F in Purified water under stirring and continued the stirring to get a clear solution.

Intra granular portion was formulated by loading Glucosamine HCl, rate controlling polymer and Calcium Hydrogen phosphate anhydrous in rapid mixer granulator and are dry mixed for 5 minutes, Povidone K90F solution was added slowly to the dry mixture and mixing was continued to get consistency of granules. The granules were dried in fluidized bed dryer and sifted through #20mesh. The granules were blended with extra granular Glucosamine hydrochloride, Microcrystalline Cellulose PH102 and Colloidal silicon dioxide for 10 minutes and lubricated with Stearic acid for 5 minutes. Then lubricated blend was compressed into tablets by Using 27 station Cadmach CMB4D d-tooling compression machine. The composition of all batches was given in Table 1.

Blend Parameters

The blend parameters like Loss on drying, Bulk density, Tapped density and Compressibility index was performed. (Ajay Bagherwal et al., 2010).

Physical parameters of compressed tablets

The physical parameters like Hardness, Friability and Weight variation was performed. (Ajay Bagherwal et al., 2010).

***In-vitro* drug release studies**

In-vitro drug release studies were conducted with six tablets per formulation using USP type II dissolution apparatus in 1000ml of purified water with the paddle speed of 50rpm. Aliquot samples were withdrawn as per the stipulated time and filtered through 0.45µM nylon filter. 2ml of the above filtrate was pipetted out into a 50ml volumetric flask and the volume was made

Table 3: In-vitro drug release data of all batches F1-F7

Time	% Cumulative Drug Release						
	F1	F2	F3	F4	F5	F6	F7
30 min	42 ±2.44	37±2.35	34 ±1.54	32±2.84	30±2.14	25±0.65	19±0.78
1st hour	70 ±2.52	65 ±1.57	58 ±1.24	50±2.62	44±2.26	43±1.38	37±0.68
2nd hour	95 ±1.26	89 ±2.64	83 ±1.62	62±2.94	52±2.64	51±1.25	40±0.67
4th hour	99 ±1.58	98 ±2.48	97 ±1.95	77±2.34	65±1.98	58±1.62	46±1.45
8th hour	98 ±1.64	100 ±3.26	101±2.87	92±2.61	81±1.65	69±1.24	59±1.48
12th hour	98 ±2.25	101±3.14	100±1.65	100±2.12	93±1.32	86±0.68	70±1.64
16th hour	100±1.79	100 ±2.48	101±1.47	101±2.64	99±1.25	91±0.98	82±1.95
20th hour	99 ±2.48	98 ±2.12	99±2.14	100±2.62	100±1.24	100±0.64	90±0.59
24th hour	99 ±2.54	98 ±2.65	97±2.58	100±2.31	98±2.41	99±0.95	99±1.23

Table 4: Kinetics data of optimized formulation F7

Formulation code	Mathematical models					
	Zero order	First order	Higuchi's model	Korsmeyer-Peppa's		Hixon-Crowell
	R^2	R^2	R^2	R^2	N	R^2
F7	0.888	0.851	0.975	0.954	0.370	0.778

Table 5: Stability data of optimized formulation F7

Name of Test	LIMIT	Initial	3rd month	6th month
Dissolution				
1st hour	NMT 40%	37±0.85	35±0.54	36±0.63
4th hour	40-50%	46±0.94	43±1.29	45±1.02
8th hour	50-65%	59±1.28	60±1.14	61±1.06
16th hour	NLT 80%	82±1.05	85±1.32	87±1.25
Assay	95-105%	100.4	99.6	99.5

with the dissolution media and mixed well. Again, 5ml of the above solution was pipetted out into 20ml volumetric flask and 2ml of derivatizing agent was added and volume was made with the dissolution media and mixed well. The absorbance of the solution was measured by using UV Spectrophotometer at 333nm.

Drug release kinetics

The *in vitro* drug release kinetics data were evaluated by using various kinetic models like Zero order, First order, Higuchi, Korsmeyer-peppas and Hixson–Crowell model to describe the release kinetics. (Hadjiioannou, TP et al., 2005; Higuchi T 1963: Hixson AW 1931).

Assay by HPLC

The optimized formulation F7 was analyzed for drug content using HPLC method at 195 nm using Waters Spherisorb Amino 250 x 4.6mm; 5micron or equivalent column at flow rate of 1.5 mL / minute and the run time was 30minutes.

Stability studies

According to ICH guidelines, the stability studies were carried out for optimized formulation F7 at accelerated condition 40°C/75% RH and Samples were withdrawn from chambers at 3rd & 6th month and analyzed for Assay and Dissolution. (Q1E Evaluation of stability data, 2006).

RESULTS AND DISCUSSION

Blend evaluation

The blend parameters of all batches were evaluated and the results confirm that the lubricated blend was very much useful for compression. The results of the blend parameters were given in Table. 2.

Tablets evaluation

The compressed tablets of all batches were evaluated for Hardness, Friability and Weight variation. The hardness of all batches of tablets were found satisfactory and all batches showed very good friability with less than 0.4% which is well within wide accepted range of pharmacopoeias limit (0.1%). The average weight of the tablets was found within acceptable limit of within 5% for all the batches. The results of compressed tablets were given in Table 2.

***In-vitro* drug release studies**

The batches F1-F3 were prepared with HPMC K100M as a controlled release polymer using wet granulation method. Initially all batches of tablets showed burst release of drug release which is due to the low concentration of controlled release polymer and at the end of 8th hour the tablets showed 98% to 100% drug release. When the concentration of polymer increases, nevertheless the tablet weight increases and becomes difficult to swallow the tablets. Because of the increased

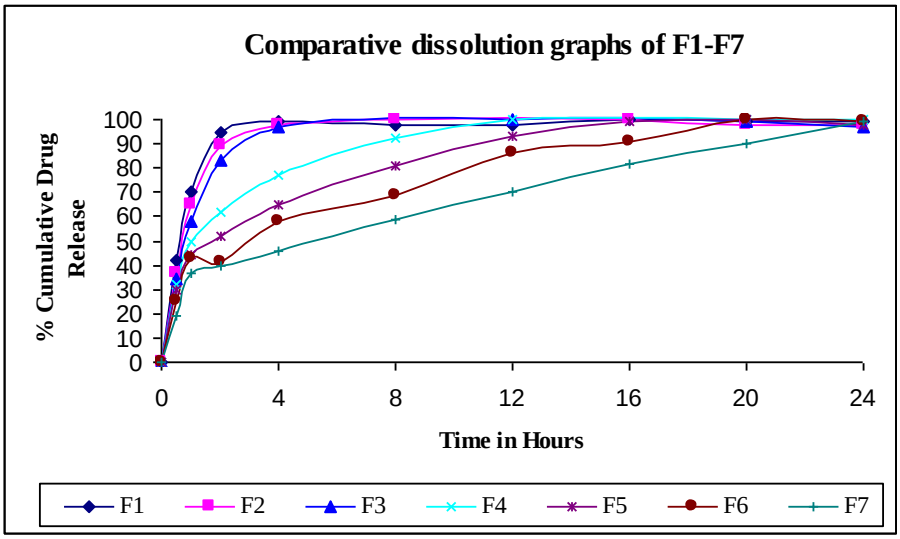

Figure 1: Comparative dissolution graphs of F1-F7

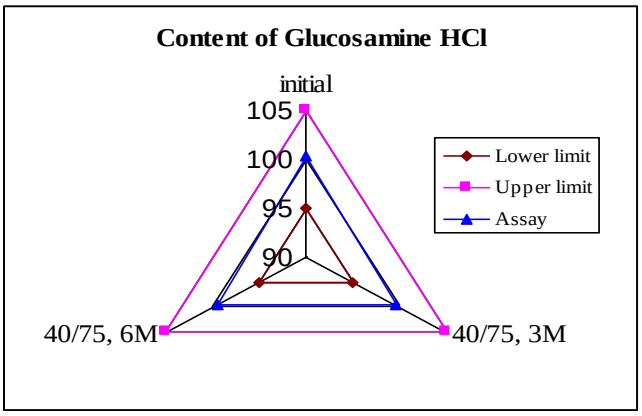

Figure 2: Content of Glucosamine HCl after 6 months stability

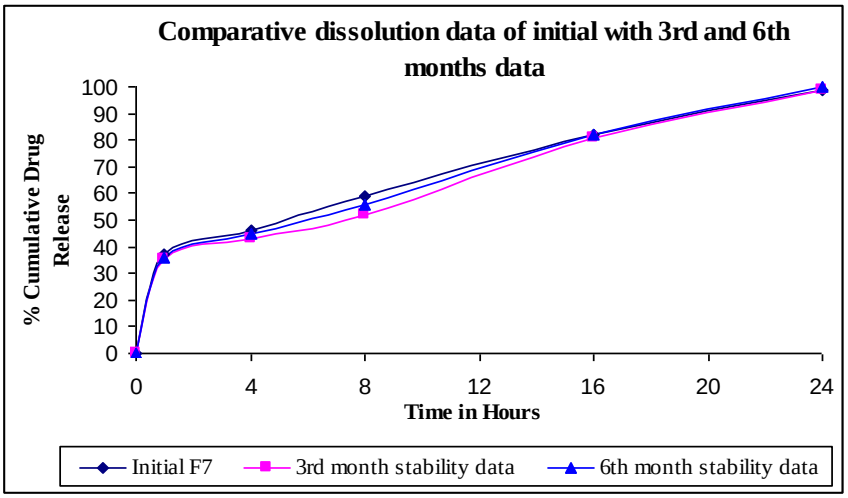

Figure 3: Comparative dissolution graph of F7 after 6 months stability

tablet weight, the further batches F4-F7 were prepared with HPMC K200M as a controlled release polymer.

The batch F4 was prepared with 45mg of HPMC K200M and it showed 100% of drug release at the end of 12hours. The bathes F5, F6 was prepared with 90mg, 135mg of HPMC K200M and it showed 100% of drug release at the end of 20hours. The finally the batch F7 was formulated with 180mg of HPMC K200M and showed 100% of drug release at the end of 24 hours. This F7 batch was showing very good control over 24hours and concluded as optimized formulation. The *in-vitro* drug release data of all batches were shown in Table 3 and the comparative dissolution graph was shown in Figure 1.

***In vitro* drug release kinetics**

Release kinetics of optimized formulation F7 was calculated and observed regression coefficients (r^2). From the observed data it was found that the drug release from the finalized batch F7 is predominant by zero order release. The regression values of all batches were shown in Table 4.

Stability studies

The optimized batch F7 samples were withdrawn at 3rd and 6th month after incubation and analyzed for assay and dissolution. From the observed stability data it was concluded that the drug was stable upto 6months period at accelerated condition and all parameters were found within the limit. The results of the same were shown in Table 5 and the graph of assay and dissolution was shown in Figure 2-3.

CONCLUSION

From the above results, it concluded that the use of simple technology achieves expected release of Glucosamine HCl and the HPMC K200M is a right choice to control the drug release for 24 hours. The stability results revealed that the composition is highly stable at accelerated conditions for a period of six months. The optimized formulation F7 can be further studied for *in vivo* bioavailability studies.

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