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FORMULATION AND DEVELOPMENT OF A BILAYER SUSTAINED RELEASED TABLETS OF ISOSORBIDE MONONITRATE

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ABSTRACT

The present study was to a develop bilayer sustained release tablet of Isosorbide mononitrate, an anti-anginal organic nitrate vasodilator. The tablets were prepared by wet granulation method. Hydrophilic and hydrophobic matrix materials such as hydroxypropyl methylcellulose, and polyox were used, which can release the drug up to 24hrs in predetermined rate. Binder used was pvp k-30. The influence of hydrophilic and hydrophobic polymer and granulation technique was studied. The formulated tablet were also characterized by physical and chemical parameters such as for granules, angle of repose, bulk density, compressibility index, total porosity, and drug content and for the tablet thickness, hardness, diameter, weight variation test, drug content, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and drug content. The in-vitro release rate profile showed the higher concentration of F6 polymer in tablet.

KEY WORDS: Isosorbide mononitrate, Bilayer sustained release tablet, hydrophilic polymer.

INTRODUCTION

Oral route is the most commonly employed route of drug administration. Although different route of administration are used for the delivery of drugs, oral route remain the preferred mode. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product.

Even for sustained release systems the oral route of administration has been investigated the most, because of flexibility in dosage forms design that the oral route offers.[1]

With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non toxic for an extended period of time[2]. To achieve better therapeutic action various types of drug delivery systems are available, out of which sustained release systems are gaining much importance because of their wide advantages over others like ease of administration, convenience and non-invasiveness.

Sustained release dosage forms cover a wide range of prolonged action preparations that provide continuous release of their active ingredients for a specific period of time. By prescribing sustained release systems, it is possible to achieve several desirable therapeutic **advantages**[2]. As the frequency of dosage is reduced, patient compliance can be improved, and drug administration can be made more convenient. The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced, because more even blood level is maintained. Total amount of drug administered can be reduced by designing sustained release systems. In addition, better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced by formulation of extended release form. The safety margin of high potency drug can be increased, and the incidence of both local and systemic adverse side effects can be reduced in sensitive patient. Overall, administration of sustained release forms enables increased reliability of therapy[3].

Isosorbide-5-mononitrate is an organic nitrate vasodilator that acts by relaxing peripheral vascular muscles and thereby reduces systolic blood pressure. The anti-anginal effect of isosorbide-5-mononitrate and other organic nitrates results from reducing myocardial oxygen demand by causing vasodilatation of the capacitance veins (to decrease pre-load), thus permitting a reduction in left ventricular volume, and energy expenditure, as well as vasodilatation of the large conductive arteries (to decrease afterload), while increasing myocardial oxygen supply by dilating epicardial coronary arteries.[4]

In man, isosorbide-5-mononitrate has an elimination half-life of 4–6 h, and shows complete bioavailability after oral administration.[5, 6] The most common dosing regimen is 20 mg two or three times daily for immediate release tablets, and 40 or 60 mg once daily for sustained-release formulations. Once daily SR 120 and 240 mg tablets have also shown their long-term efficacy in stable effort angina up to 12 h post-dose without rebound (zero-hour effect).[7] The efficacy of multiple-dose and once daily dosing were not different but the latter regimen was found to provide a better quality of life in large-scale studies.[8, 9]

In the present work an attempt has been made to formulate an antiangianl drug which will give faster onset of action along with sustained effect. For this purpose a bilayer tablet has been formulated, of which the upper layer is a conventional tablet which is termed as 'Immediate Release' (IR) layer and the lower layer is a 'Sustain Release' layer. The goal for developing this new drug delivery tablet containing 50mg IR layer and 150mg of SR layer tablet of isosorbide-5-mononitrate, was to obtain a formulation exhibiting good absorption, with sufficiently high plasma levels during most part of the day followed by a lower concentration phase in order to prevent nitrate tolerance, while producing a sufficiently long duration of action to allow a once daily regimen. This technique was used because of the various advantages it offers. For the sustain release layer it was intended to use two different polymers to formulate a polymer matrix systems namely Hydroxypropylmethylcellulose and Polyox WSR 303. The drug release pattern from both these matrices was studied.

FORMULATION OF THE BILAYER SUSTAINED RELEASE TABLETS:

Formulation of Immediate Release (IR) layer of the tablet:

An immediate release layer of the tablet was formulated using wet granulation method. Different formulations were made in order to achieve desired disintegration time, drug release, friability, thickness and hardness.

Preparation of the Immediate Release granules:

- Sifting: The Drug, MCC PH101, Croscarmellose sodium, Sodium Lauryl

Sulphate, and color were sifted through sieve # 40.

- Mixing: The sifted ingredients were mixed thoroughly in a polybag for 15min.
- Preparation of Binder: PVP K-30 was dissolved in boiling water, simultaneously maize starch was dispersed in water and added to the PVP K-30 solution with stirring till the desired consistency was achieved.
- Preparation of Granules: The prepared paste was added to the sifted and mixed powder slowly till the desired wet mass was formed. This wet mass was sifted through sieve #10.
- Drying: The prepared granules were dried in an oven at 55^0C for 2 H and sifted through sieve #20. Loss on drying was done.
- Lubrication: Cab-O-Sil, Croscarmelose sodium and Magnesium stearate were sifted through sieve #60 and mixed with the prepared granules in a polybag for 5min.

Formulation of Sustained Release (SR) layer of the tablet:

A Sustain release layer of the tablet was formulated using swellable polymers and non aqueous granulation method. The tablets were of matrix type made in order to achieve desired thickness, hardness and drug release. The details are given below:

Preparation of Sustain Release granules:

- Sifting: The Drug, MCC PH101 and Polymer were sifted through sieve # 40.
- Mixing: The sifted ingredients were mixed thoroughly in a polybag for 15min.
- Preparation of Binder: PVP K-30 was dissolved in Isopropyl alcohol with stirring till a clear solution was obtained.
- Preparation of Granules: The prepared paste was added to the sifted and mixed powder slowly till the desired wet mass was formed. This wet mass was sifted through sieve #10.
- Drying: The prepared granules were dried in an oven at 45^0C for 2 H and sifted through sieve #20. LOD was done.
- Lubrication: Magnesium stearate and cab-o-sil was sifted through sieve #60 and mixed with the prepared granules in a polybag for 5min.

COMPRESSION OF THE BILAYER TABLET:

The prepared granules of both the layers were compressed on a Cad Mac Double Rotary Bilayer compression machine on 11mm flat round shaped punch. The hardness was 8-9kg/cm^2 and the tablet thickness was 3.8 - 4.0mm. Both the prepared granules came from two different hoppers to two different feed frames where they occupied the die cavity. The bottom layer was first compressed with lower pressure, which was then followed by filling of the die cavity by the upper layer granules. The final compression was done only after both the granules occupied the die cavity one on top of the other. Both the layers were identified on the basis of color since the immediate release layer had pink color and the sustain release layer has white color.

FORMULAE FOR OPTIMIZING THE DOSE OF THE DRUG IN BOTH THE LAYERS OF THE TABLET

Different formulations were made in order to achieve the desired drug release from the bilayer tablet. The formulae were as follows.

Table 12
Different formulations of drug in both the layers, polymer quantity along with quantity of Microcrystalline cellulose PH101.

Ingredients	Weight in mg		
	A	B	C
Immediate Release Layer			
Isosorbide mononitrate	70	60	50
Microcrystalline cellulose PH 101	34.8	44.8	54.8
Weight (mg) IR layer	160	160	160
Sustain Release layer			
Isosorbide mononitrate	130	140	150
MCC PH101	75	65	55
HPMC K4M	70	70	70
Weight(mg) SR layer	300	300	300
Total Tablet Weight (mg)*	**460**	**460**	**460**

*All other excipients and their quantities were kept constant.

FORMULATION OF BATCHES OF OPTIMIZED DOSE OF BILAYER TABLET

The various formulations were prepared by varying the quantity of polymers and also by using different polymers to study the dissolution profiles. The manufactured tablets were evaluated mainly for thickness, hardness and percent drug release.

Table 1
Formulation development of immediate release layer

Ingredients	FORMULATIONS (mg)						
	F1	F2	F3	F4	F5	F6	F7
Isosorbide mononitrate	50	50	50	50	50	50	50
MCC PH 101	54.8	52.8	52.8	52.8	52.8	52.8	52.8
Croscarmellose Sodium USPNF	7	7	7	7	7	7	7
Colour Carmosine	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium lauryl sulphate	5	5	5	5	5	5	5
Povidone	15	15	15	15	15	15	15
Maize starch	15	15	15	15	15	15	15
Croscarmellose Sodium USPNF	7	7	7	7	7	7	7
Cab-O-Sil	3	3	3	3	3	3	3
Magnesium Stearate	5	5	5	5	5	5	5
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Weight (mg) IR	160	160	160	160	160	160	160

Table 2
Formulation development of sustained release layer

Ingredients	FORMULATIONS (mg)						
	F1	F2	F3	F4	F5	F6	F7
Isosorbide mononitrate	150	150	150	150	150	150	150
HPMC K4M	70	60	58	55	--	--	--
Polyox WSR 303	--	--	--	--	40	45	50
MCC PH 101	55	60	62	65	80	75	70
PVP K30	20	20	20	20	20	20	20
Magnesium stearate	10	10	10	10	10	10	10
Isoproply alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Cab-o-sil	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Weight(mg) SR	300	300	300	300	300	300	300
Total Tablet Weight (mg)	**460**	**460**	**460**	**460**	**460**	**460**	**460**

Table 3
Evaluation of Isosorbide mononitrate sustained release tablet

Formulations	Hardness Kg/cm^2	Thickness mm	Friability %	Weight uniformity Mg	Drug content (%)
F1	8-9	4.06±0.08	0.54±0.03	460±0.45	101.75±1.83
F2	8-9	3.86±0.04	0.55±0.05	464±0.89	100.69±1.32
F3	8-9	4.07±0.04	0.57±0.04	459±0.98	101.28±2.43
F4	8-9	4.01±0.06	0.52±0.02	462±0.08	98.58±1.49
F5	8-9	4.05±0.03	0.40±0.03	461±0.19	100.93±1.33
F6	8-9	3.95±0.05	0.41±0.02	460±0.45	99.58±1.49
F7	8-9	4.12±0.07	0.37±0.05	460±0.71	98.43±0.79

In vitro Dissolution Studies:

The study was carried out using Distilled water using USP apparatus type 2, the dissolution medium 500 ml maintained at 37°c ± 0.5°c, the dissolution study were carried out for 24hrs[10]. The absorbance was measured at 220nm

A) Evaluation of granules: [11, 12, 13]

Granules prepared by wet granulation method were evaluated for bulk density, angle of repose and drug content.

Bulk Density/Tap Density of the Drug [14, 15]

Bulk density of the drug API was carried out using bulk density apparatus. Weight of an empty cylinder was taken. Drug was poured in to the cylinder and the volume was measured. The cylinder was kept in the apparatus and tapped for 100 times. The final volume after 100 taps was measured. Then the following calculations were made:

Loose Bulk Density (LBD) = weight of powder/ volume of packing

Tap Bulk Density (TBD) = weight of powder/ tapped volume of packing
Carr's Index = [(TBD. – LBD) x 100] / TBD
Hausners Ratio = Initial volume / Final volume

b) Angle of repose:

The angles of repose of the granules were determined by using funnel method. The accurately weighted granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated by using the equation

$\tan\theta = h/r$

Where, h and r are the height and radius of the powder cone.[16]

Drug content:

An accurately weighed amount of powder isosorbide mononitrate granules (100mg) was extracted with water and the solution was filtered through 0.45μ membrane. The absorbance was measured at 220 nm after suitable dilution.[17]

EVALUATION OF SUSTAINED RELEASED TABLETS [11, 12, 13]

Tablet Thickness and Size

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using vernier calliper[18].

Tablet Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm^2.[19]

Friability

Friability is the measure of tablet strength. Electrolab EF-2 friabilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm droAPIng the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.[20]

% loss = [(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] ×100

Uniformity of Weight

Twenty tablets were selected at random and the average weight was calculated. Weight variation was calculated and was compared with I. P. standards.[21]

RESULT AND DISCUSSION

Evaluation of the Tablet batches A, B, C which were formulated to determine the dose of the drug in both the layers of the tablet.

Formulations A, B and C were formulated to optimize the dose of the drug in both the layers of the bilayer tablet formulation. The ratio of the drug in both the layers was optimized in order to obtain satisfactory In-vitro dissolution profiles. Formulations A, B, C were evaluated for various physical properties such as tablet weight, drug content, hardness, thickness, % friability and the results are follows.

Table 18

Evaluation results of tablet batches A, B and C.

Formulations	Tablet Weight (mg)	Hardness kg/cm^2	Thickness † (mm)	% Friability‡	Drug Content*
A	461±0.45	8-9	3.92±0.04	0.82±0.04	99.40±1.26
B	458±0.12	8-9	4.09±0.06	0.92±0.06	102.80±1.66
C	465±0.69	8-9	4.16±0.03	0.70±0.04	98.86±0.33

†- n=10, ‡- n=20 , *-n=10

In vitro dissolution studies of formulations A, B, C.

The *in vitro* drug release characteristics were studied in distilled water for a period of 24 h using USP type II dissolution apparatus. The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in a predetermined manner.

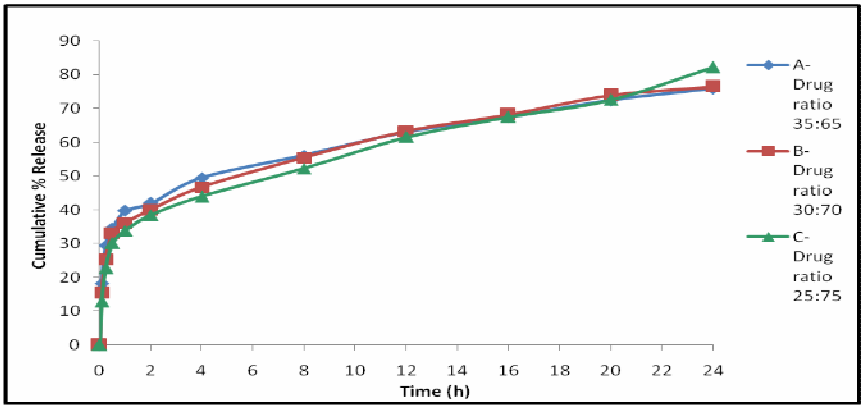

Figure 14
Comparative dissolution profiles of formulation A, B and C.

Formulations A, B and C were formulated to optimize the dose of drug in both the layers. The drug release pattern from the three formulations reveled that when the drug was divided in the ratio of 35 : 65 (formulation A) the initial drug release was after 30 min was 34.42%w/w and at the end of 24h was 75.83% w/w. In order to observe greater percent release at the end of 24h the dose in the immediate release layer was reduced and added to the sustain release layer. Hence the formulation B had the ratio 30:70 of drug distribution. In this formulation it was observed that the drug released from the tablet was reduced in the first 30min and increased later. The drug release after 24h was found to be 76.47%w/w. The drug release desired at the end of 24h was more than 80%w/w and in the first 30min was around 30%w/w. Hence the dose from the immediate release layer was further decreased and added to the sustain release layer. The formulation C now contained drug distributed in the ratio 25:75. The drug release observed from this formulation was observed 30.07%w/w in the first 30 min and at the end of 24h the release was 82.22%w/w. So the concentration 50 mg of drug in the immediate release layer and 150 mg in sustain release layer was optimized.

Evaluation of batches of optimized dose of bilayer tablet

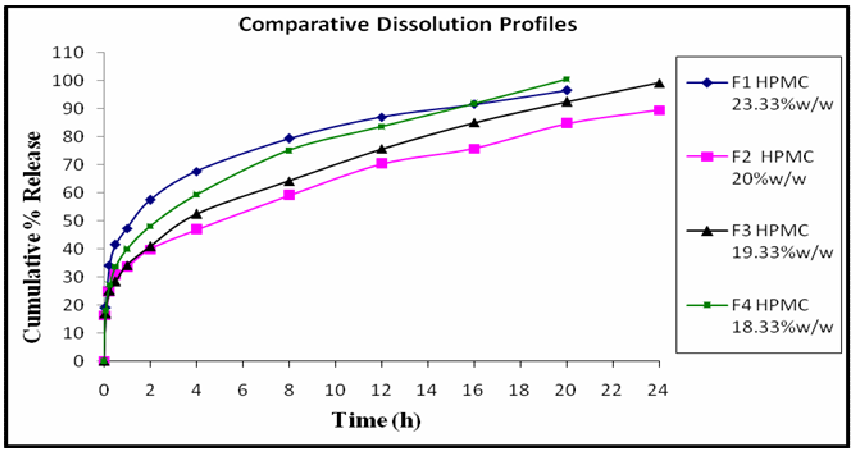

Figure 1
Comparative dissolution profiles of formulation F1, F2, F3 and F4.

Formulations F1, F2, F3 and F4 were formulations prepared by using HPMC K4M. The quantity of HPMC was varied to achieve the desired drug release profile. In F1 the quantity of HPMC was 23.33%w/w which gave drug release of 84.73%w/w after 24h. In order to achieve greater drug release the quantity of HPMC was reduced to 20%w/w. this was formulation F2 which showed drug release of 89.517%w/w at the end of 24h. When quantity of HPMC was further reduced to 19.33%w/w (F3) and 18.33%w/w (F4) the drug release from the formulation was found to be 99.26%w/w after 24h and 100.48%w/w after 20h.

The formulation F3 containing 19.33%w/w of HPMC was selected as the optimized batch since it showed the best drug release profile as compared to the other formulations of HPMC K4M. All the other parameters of the batch F3 were found to be satisfactory. Hence it was selected for further stability studies.

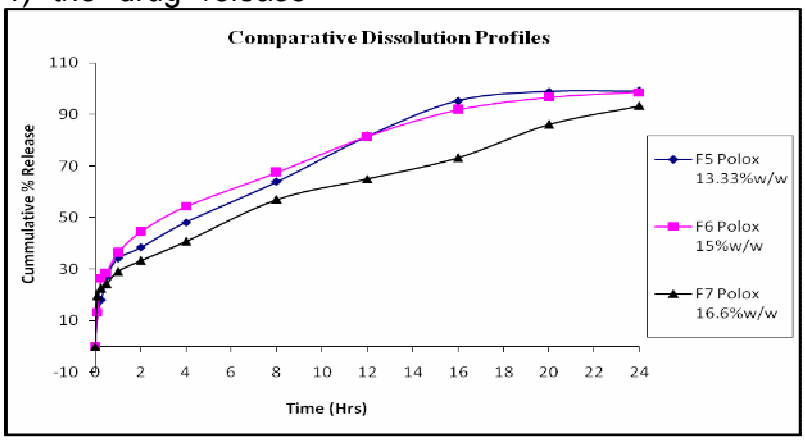

Figure 2
Comparative dissolution profiles of formulation F5, F6 and F7.

Polyox WSR 303 was another polymer which was used to study the release of the Isosorbide mononitrate for the tablet formulation. 3 formulations F5, F6 and F7 containing 13.33%w/w, 15%w/w and 16.33%w/w respectively were formulated. The drug release form these formulation showed that at the end to 20h, F5 showed 98.911%w/w, F6 showed 96.599%w/w and F7 showed 86.177%w/w. Comparing the overall drug release profiles F6 was found to be the best with 28.69%w/w drug release after 30min and 98.57%w/w drug release after 24h.

Hence formulation F6 containing 15%w/w of Polyox WSR303 was selected for the further stability studies.

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