Preparation and Evaluation of Extended-Release Matrix Tablets of Antiviral Drugs Zidovudine and Nevirapine

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Abstract

Zidovudine and Nevirapine are widely used antiviral drugs in the management of HIV infection. Both drugs require frequent administration due to relatively short half-life and pharmacokinetic limitations, leading to poor patient compliance and dose-related adverse effects. The present investigation was undertaken to develop extended release (ER) matrix tablets of Zidovudine (300 mg) and Nevirapine (400 mg) using hydrophilic polymer Hydroxypropyl Methylcellulose (HPMC) by wet granulation technique. Solid state characterization of both APIs was performed using FTIR, XRD, DSC and DVS studies. Drug–excipient compatibility studies were conducted under stressed conditions. Formulation trials were designed using different grades and concentrations of HPMC. For Nevirapine ER tablets, Quality by Design (QbD) approach was implemented by defining QTPP and identifying CQAs, CMAs and CPPs. Tablets were evaluated for pre-compression and post-compression parameters and subjected to in vitro dissolution studies in appropriate dissolution media. Optimized Zidovudine formulation (ZID/11) showed sustained drug release up to 20 hours following Higuchi kinetics with anomalous diffusion mechanism. Nevirapine ER tablets matched the innovator dissolution profile in multi-media conditions. Stability studies as per ICH guidelines demonstrated that all impurities were within acceptable limits. The study concludes that hydrophilic matrix systems using HPMC are suitable for developing stable and effective extended release formulations of antiviral drugs.

INTRODUCTION

Oral drug delivery remains the most preferred route of drug administration because of patient convenience, ease of manufacturing and economic advantages. Tablets are the most widely accepted oral dosage forms; however, conventional immediate release formulations often result in fluctuations in plasma drug concentration, leading to sub-therapeutic or toxic levels. Extended release (ER) formulations are therefore developed to maintain drug concentration within the therapeutic window for prolonged periods, thereby reducing dosing frequency and improving patient compliance (Chien, 1992; Vyas and Khar, 2002).

Modified release dosage forms are defined as formulations in which drug release characteristics are altered to achieve therapeutic or convenience objectives not offered by conventional dosage forms (Malinowski and Marroum, 1999). According to the United States Pharmacopeia, ER dosage forms allow at least a twofold reduction in dosing frequency compared to conventional dosage forms (FDA, 1997). The primary objective of ER systems is to maintain drug concentration above the minimum effective concentration (MEC) and below the maximum safe concentration (MSC) for an extended duration (Aulton, 2002).

Matrix systems are widely used ER systems due to their simplicity, ease of manufacturing and cost effectiveness. Drug release from hydrophilic matrices is generally governed by diffusion, polymer swelling and erosion mechanisms (Colombo et al., 2001). Hydroxypropyl methylcellulose (HPMC) is one of the most commonly used hydrophilic polymers in ER formulations because of its gel-forming ability, reproducible drug release profile and regulatory acceptance (Chatlapalli and Rohera, 1998).

Zidovudine is a nucleoside reverse transcriptase inhibitor used in HIV therapy. It exhibits a short biological half-life of approximately 3–4 hours, requiring frequent administration and potentially leading to dose-related adverse effects (Chitnis et al., 2002). Nevirapine is a non-nucleoside reverse transcriptase inhibitor belonging to BCS Class II and demonstrates solubility-limited absorption characteristics (Re et al., 2003). Development of ER formulations for these antiviral drugs may reduce dosing frequency, improve therapeutic efficacy and enhance patient adherence.

Therefore, the present study was undertaken to develop and evaluate extended release matrix tablets of Zidovudine and Nevirapine using hydrophilic HPMC polymers and to optimize the formulation variables for improved controlled drug release.

MATERIALS AND METHODS

Materials

Zidovudine and Nevirapine were obtained from approved manufacturers. HPMC K4M and K15M premium CR, microcrystalline cellulose, lactose monohydrate, magnesium stearate and Opadry were used as excipients

Solid State Characterization

APIs were characterized by optical microscopy, FTIR, XRD, DSC and DVS analysis. Stress stability studies were performed under 40°C/75% RH and 50°C conditions

Drug–Excipient Compatibility

Physical mixtures of drug and excipients were stored under stressed conditions and analyzed for impurity profile by HPLC.

Preparation of ER Matrix Tablets

Zidovudine ER tablets were prepared using wet granulation technique after failure of dry granulation due to processing defects. Nevirapine ER tablets were developed based on innovator characterization and QbD approach. Granules were dried, milled and compressed using rotary tablet press.

Evaluation of Tablets

Pre-compression parameters included bulk density, tapped density, angle of repose and compressibility index. Post-compression evaluation included hardness, thickness, friability, weight variation and assay.

In Vitro Dissolution Study

Dissolution studies were performed using USP apparatus I or II under specified media conditions. Zidovudine ER tablets were compared with IR tablets. Nevirapine ER tablets were evaluated in multi-media (pH 1.2, 4.5, 7.8 with 2% SLS)

Stability Studies

Optimized formulations were stored at 40°C/75% RH for 3 months and analyzed for assay and impurities as per ICH guidelines

RESULTS & DISCUSSION

Table 1 Initial Trial Batches (Dry Granulation)

Sr.No.	Ingredients (mg/tablet)	Batch No.	
		ZID/01	ZID/02
1	Zidovudine	300.00	300.00
2	HPMC K4M	50.00	-
3	HPMC K15M	50.00	80.00
4	HPMC K100M	-	45.00
5	MCC PH 112	97.00	97.00
6	Magnesium stearate	3.00	3.00

Table 2 Initial Trial Batches (Wet Granulation)

Sr.No.	Ingredients	Batch No			
		ZID/03	ZID/04	ZID/05	ZID/06
	mg/tab				
	Polymer ratio	16%	16%	16%	16%
Intragranular					
1	Zidovudine	300.00	300.00	300.00	300.00

2	HPMC K4M CR	-	40.00	50.00	55.00
3	HPMC K15M CR	35.00	30.00	20.00	15.00
4	HPMC K100M CR	35.00	-	-	-
5	MCC PH 101	28.00	28.00	28.00	28.00
Granulating fluid					
6	Isopropyl alcohol	q.s.	q.s.	q.s.	-
7	Purified water	-	-	-	q.s.
Extragranular					
8	MCC PH 102	20.00	20.00	20.00	20.00
9	Magnesium stearate	2.00	2.00	2.00	2.00
	Total weight	420.00	420.00	420.00	420.00

Table 3 Design Batches of Zidovudine ER Matrix Tablets Batch Size-2000 Units

| Sr.No.	Ingredients (mg/tablet)	ZID/07	ZID/08	ZID/09	ZID/10	ZID/11
	Polymer Ratio	25 %	20 %	25 %	20 %	25 %
Intragranular						
1	Zidovudine	300.00	300.00	300.00	300.00	300.00
2	HPMC K4M premium CR	-	-	80.00	70.00	80.00
3	HPMC K15M premium CR	80.00	70.00	-	30.00	45.00
4	HPMC K100M premium CR	45.00	30.00	45.00	-	-
5	MCC PH 101	60.00	85.00	60.00	60.00	60.00
Granulating Fluid						
6	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Extragranular						
7	MCC PH 102	12.00	12.00	12.00	12.00	12.00
Lubricants						
8	Magnesium stearate	3.00	3.00	3.00	3.00	3.00
	Average wt. core	500.00	500.00	500.00	500.00	500.00
Coating						
9	Opadry Y-1-7000	20.00	20.00	20.00	20.00	20.00
10	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
	Average wt. coated	520.00	520.00	520.00	520.00	520.00
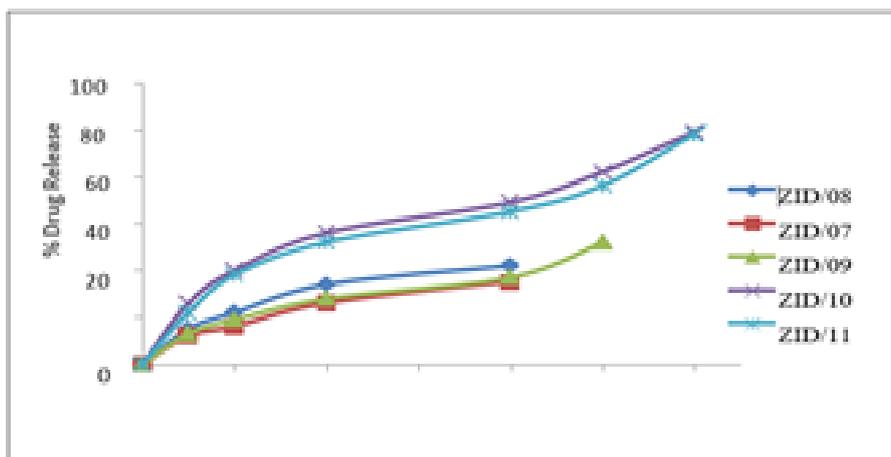
Fig.1: Dissolution Profile

Table 4: Final Composition Zidovudine ER Matrix Tablet 300 mg

Component	Qty. per unit (mg)	Function	Reference to quality standard
Intragranular			
Zidovudine	300.00	Active pharmaceutical Ingredient	USP -NF
Hypromellose (K4M premium CR)	80.00	Polymer	USP- NF + IH
Hypromellose (K15M premium CR)	45.00	Polymer	
Microcrystalline cellulose (Avicel PH 101)	70.00	Diluent	USP- NF + IH
Binder solution			
Purified water	q.s.	Granulating fluid	
Extra granular			
Microcrystalline cellulose (Avicel PH 102)	12.00	Coloring agent	USP- NF +IH
Lubrication			
Magnesium stearate	3.00	Lubricant	USP- NF + IH
Core tablet weight	**500.00**		
Coating			
Opadry white Y-1-7000	20.00	Coating material	IH
Purified water	q.s	Coating fluid	
Coated tablet weight	520.00		

Table 5: Compression Parameters at Different Run Time

Parameters	Start	Middle	End
Physical attributes	Satisfactory	Satisfactory	Satisfactory
Individual wt. (mg)	492 - 512	491 – 508	490 – 511
Hardness (N)	145	155	148
Thickness (mm)	4.95 - 5.11	4.97 - 5.08	4.94 - 5.10
Friability (%) 300 rpm	0.341	0.228	0.318
Content Uniformity (%)			
Mean	99.18	98.12	98.47
Min.	97.12	95.12	98.20
Max.	101.00	99.50	101.20
% RSD	2.12	2.5	1.98
Conclusion	All compression parameters were well within the limits throughout the compression run.		

Stability Study

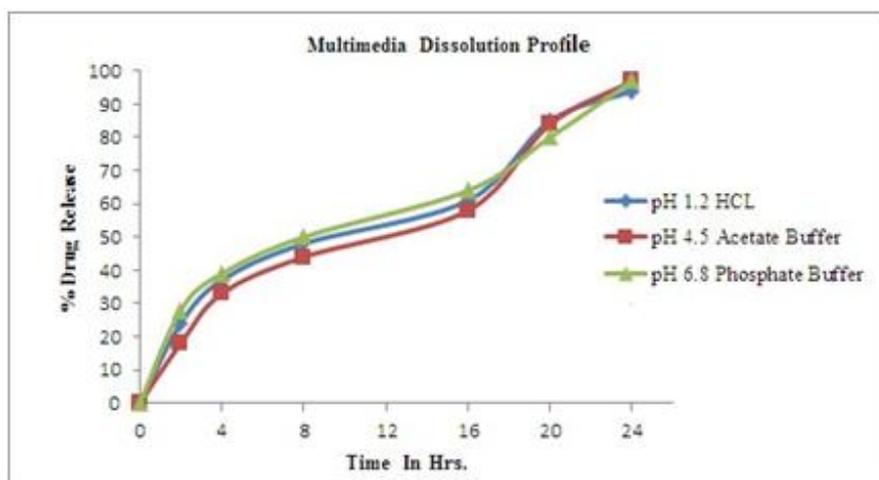| Condition Batch No.	Pack	Impurity			Unk. Impurity	Assay
		C	A	B		
Initial (ZID/SCA/01)		0.10	0.05	BLOQ	0.08	99.45
1 Month 40ºC/75% RH	Alu-Alu	0.12	0.09	0.04	0.12	99.01
2 Months 40ºC/75% RH		0.14	0.11	0.07	0.12	98.80
3 Months 40ºC/75% RH		0.17	0.12	0.08	0.14	98.50

Fig.2: Multimedia Dissolution Profile of Zidovudine ER Matrix Tablet

DISCUSSION

Solid state characterization confirmed purity and stability of both APIs. No significant polymorphic transitions were observed. Compatibility studies showed no significant increase in impurities under stressed conditions. Wet granulation method provided robust processing and acceptable physical characteristics for Zidovudine ER tablets. Polymer concentration significantly influenced drug release rate. Optimized batch ZID/11 followed Higuchi model (r^2 = 0.991) indicating diffusion-controlled release. In vivo study in rabbits demonstrated reduced Cmax and prolonged Tmax for ER tablets compared to IR formulation, confirming sustained drug delivery. For Nevirapine ER tablets, QbD approach enabled systematic identification of critical material attributes and process parameters. Multi-media dissolution studies confirmed similarity with innovator profile. Reverse engineering using ATR-IR confirmed polymer level and API distribution. Stability studies indicated that optimized formulations remained stable with impurities within ICH limits.

CONCLUSION

Extended release matrix tablets of Zidovudine and Nevirapine were successfully developed using hydrophilic HPMC polymer. Wet granulation technique was found suitable for manufacturing robust ER matrix tablets. Zidovudine optimized batch demonstrated sustained release up to 20 hours with diffusion and erosion mechanism. Nevirapine ER tablets

developed using QbD approach matched innovator dissolution profile and met quality requirements. Stability studies confirmed formulation stability under accelerated conditions. The developed ER formulations offer potential benefits in reducing dosing frequency, improving compliance and minimizing dose-related adverse effects in HIV therapy.

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CONFLICT OF INTERESTS

The authors declare no conflict-of-interest

ETHICS APPROVAL

Not applicable

FUNDING

AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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