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Formulation and evaluation of Zolmitriptan controlled release matrix tablets

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ABSTRACT

Controlled release formulations in many case provide significant advantages, including improved therapeutic effect, increased patient compliance by reducing dosing frequency and decrease in incidence and or intensity of adverse effect by a constant blood concentration. The main objective of the present study was to develop controlled release matrix tablet formulation containing 5mg of Zolmitriptan for the treatment of migraine.

The prepared tablets were then subjected to dissolution test for evaluating the in vitro drug release. The dissolution studies were carried out in 0.1 N HCl in USP II apparatus at 37±0.5°C. The results of the dissolution studies indicated that the polymer concentration was having a substantial effect on the drug release from the tablets. Formulation F14 which contained HPMC K15 (20%) and CAP have better controlled drug release (99.7% at 12 hours) and in comparison to the other formulations.

1. INTRODUCTION

Zolmitriptan is an oral antimigrane agent, which is a commonly prescribed for the treatment of patients with migrane attacks. Zolmitriptan is a weak base (pKa = 9.6). Soluble in water and 0.1N HCl acid environment and highly soluble less permeable (class III) drugs according to the Biopharmaceutical Classification System (BCS).

The oral absorption is uniform, slow with a bioavailability of nearly 40% and reported to have a short biological half-life (3±0.6 hrs) requiring it to be administered in 2 to 3 doses of 2.5 to 5mg per day. CR formulations that would maintain plasma levels of drug 8 to 12 hrs might be sufficient dosing for Zolmitriptan. SR products are needed for Zolmitriptan to prolong its duration of action and to improve patience compliance.

The polymer selected for the present work was Hydroxypropyl methylcellulose (HPMC) K4M, K15M, K100M Grades, and combination with Ethyl cellulose (EC), and Cellulose Acetate phthalate (CAP). The effect of polymer types and drug: polymer ratio on release also studied. Hydrophilic polymer matrix system are widely used for designing oral controlled release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and a broad regulatory acceptance.

In this formulation method combination of Ethyl cellulose and Cellulose acetate phthalate with different grades of HPMC K4M, K15M, K100M were used to control the drug release from the polymer. Formulation with these polymers will leads to slow release of drug from the polymer matrix either by diffusion or by dissolution method following drug kinetic release.

Formulation of Zolmitriptan in the form of matrix tablets leads to prolonged action of drug where the drug binds to the receptor site and drug released from the matrix slowly either in the diffusion or dissolution process and shows action on the target site for long time.

2. MATERIALS AND METHODS

Zolmitriptan was procured from Reddys labs Ltd, Hyderabad, HPMC K4M, HPMC K15M and HPMC K100M were purchased from Colorcon Asia Pvt Ltd. EC and CAP were purchased from Signet chemicals. Lactose fromVilin Bio med Ltd, Roorkee, India.

Preformulation and drug excipient compatibility studies were conducted. Drug excipient compatibility studies were conducted by using FTIR.

Formulation development: Zolmitriptan matrix tablets were prepared by mixing manually in poly bags with different viscosity grades of HPMC such as HPMC K4M, HPMC K15M, HPMC K100M and in combination with EC and CAP. Tablets were prepared by direct compression method to observe the in vitro dissolution of drug from HPMC polymers at different concentration such as 10%, 20%, 30% to the target

weight (100 mg) which was kept constant in all formulation F1 to F15. Accurately weighed quantity of drug, polymer and lactose were directly mixed uniformly and then the mixed blend was pre-lubricated with talc and Aerosil and finally lubricated with magnesium stearate manually in polybags for 5-10 min. The concentration of the HPMC K4M, HPMC K15, HPMC K100 in different formulation are (10%), (20%), (30%). The lubricated blend was evaluated for precompression parameter to determine the flow property of the powder and compressed into tablet by using 6.0mm punch.

Table.1.Formulation composition of Zolmitriptan tablets (qty. in mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Zolmitriptan	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
HPMC K4M	10	20	30	-	-	-	-	-	-	-	-	30	-	-	30
HPMC K15M	-	-	-	10	20	30	-	-	-	-	20	-	-	20	-
HPMC K100M	-	-	-	-	-	-	10	20	30	10	-	-	10	-	-
Cellulose acetate Pthalate	-	-	-	-	-	-	-	-	-	-	-	-	5	5	5
Ethyl cellulose	-	-	-	-	-	-	-	-	-	5	5	5	-	-	-
Lactose	79.25	69.25	59.25	79.25	69.25	59.25	79.25	69.25	59.25	79.25	69.25	54.75	79.25	69.25	59.25
Aerosil	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Total weight	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

***In-vitro* dissolution study:**

Table.2.*In-vitro* dissolution study

Apparatus	Dissolution test apparatus (USP XXIII)
Method	USP type 2 apparatus (paddle method)
Dissolution medium	0.1N HCl
Volume	500ml
Temperature	37 ± 0.5 ^{0} C
Speed	50 rpm

Procedure: The tablet was placed inside the dissolution vessel. 5ml sample were withdrawn at time intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hours. The volume of dissolution fluid adjusted to 500 ml replacing fresh 5 ml of dissolution medium after each sample withdrawing. The release studies were conducted with 3 tablets and the mean value were plotted vs time. Each sample were analyzed at 283nm. The drug concentration was calculated using standard calibration curve.

3. RESULTS AND DISCUSSION

Acceptable physiochemical properties were observed for the prepared matrix tablets. F1 to F3 which is containing HPMC K4 (10%, 20%, 30%). Friability of the prepared matrix tablets F1, F2, F3 was (0.40, 0.54, 0.65%) respectively, Indicating that friability is within the acceptable limits. Hardness of the tablets was found to be good depending up on compression force applied (4-6.9 kg/cm2). The thickness of the tablets were found to be in the range of (2.42mm-2.63 mm).All the formulation shown uniform thickness which indicates good mechanical strength of the tablet. Drug content of the prepared matrix tablets was found to be in the range of 98.12-98.48%. Which is in the range as per the requirement of pharmacopoeia.

Acceptable physiochemical properties were observed for the prepared matrix tablets. F4 to F6 which contain HPMC K15 10%, 20%, 30% respectively.Friability of the prepared matrix tablets was (0.36%,0.40%,0.36%). Indicating that friability is with in the acceptable limits. Hardness of the tablets was found to be good depending up on compression force applied (6.9-7 kg/cm2). The thickness of the tablets were found to be in the range of (2.54mm-2.60mm).All the formulation shown uniform thickness which indicates good mechanical strength of the tablet. Drug content of the prepared matrix tablets was found to be in the range of 98.5-99.8%. which is in the range as per the requirement of pharmacopoeia.

Acceptable physiochemical properties were observed for the prepared matrix tablets. Friability of the prepared matrix tablets was (0.38%, 0.36%, 0.38 %),F7 to F9 which contain HP mc k100 10%,20%,30% respectively indicating that friability is with in the acceptable limits. Hardness of the tablets was found to be good depending up on compression force applied (6-6.6kg/cm2). The thickness of the tablets were found to

be in the range of (2.50mm-2.64mm).All the formulation shown uniform thickness which indicates good mechanical strength of the tablet. Drug content of the prepared matrix tablets was found to be in the range of 98.56-101%, which is in the range as per the requirement of pharmacopoeia.

Acceptable physiochemical properties were observed for the prepared matrix tablets F10 to F11 contained combination of Hpmck10010%, K1520%, K430% with ethyl cellulose. Friability of the prepared matrix tablets was (0.41%, 0.31%, 0.41%). Indicating that friability is within the acceptable limits. Hardness of the tablets was found to be good depending up on compression force applied (6.6-6.7 kg/cm2). The thickness of the tablets were found to be in the range of (2.42mm-2.58mm).All the formulation shown uniform thickness which indicates good mechanical strength of the tablet. Drug content of the prepared matrix tablets was found to be in the range of 100-101%, which is in the range as per the requirement of pharmacopoeia.

Acceptable physiochemical properties were observed for the prepared matrix tablets F12 to F15 which contained combination of HPMC k10010%, K1520%, K430% with cellulose acetyl phalate Friability of the prepared matrix tablets was (0.31, 0.33, 0.36%). Indicating that friability is within the acceptable limits. Hardness of the tablets was found to be good depending up on compression force applied (6.6-6.9 kg/cm2). The thickness of the tablets were found to be in the range of (2.40mm-2.42mm).All the formulation shown uniform thickness which indicates good mechanical strength of the tablet. Drug content of the preparedmatrix tablets was found to be in the range of 99.9.-100.1%.

Table.3.Physical parameters of the prepared Zolmitriptan matrix tablet

Formulation Code	Weight variation (mg)	Thickness (mm)	Tablet hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	98.9±0.33	2.42±0.66	6.2±0.44	0.40	98.12±1.2
F2	97.5±1.31	2.52±0.08	6.3±0.46	0.54	98.2±0.2
F3	99.2±1.42	2.63±0.09	6.9±0.54	0.65	98.48±0.62
F4	100.2 ±1.33	2.54±0.09	6.9±0.05	0.36	98.5±0.96
F5	99.5 ±1.37	2.48±0.09	6.2±0.43	0.40	97.25±0.86
F6	98.9±1.39	2.60±6.08	7±0.16	0.36	99.1±0.05
F7	101.2±1.45	2.50±0.08	6 ±0.51	0.38	98.2±0.097
F8	102±1.32	2.57±0.06	7.3±0.45	0.36	99.56±0.097
F9	99.5±1.35	2.64±0.09	6.6±0.52	0.38	98.56±0.91
F10	98.2±1.42	2.58±0.094	6.7±0.54	0.41	101±0.082
F11	99.5±1.35	2.42±0.081	6.6±0.51	0.31	100.1 ±0.091
F12	98.2±1.42	2.58±0.091	6.7±0.54	0.41	101±0.082
F13	99.8±1.35	2.42±0.081	6.6±0.51	0.31	100.1±0.091
F14	101±1.5	2.40±1.38	6.9±0.51	0.33	101.2±1.2
F15	101±1.5	2.40±1.38	6.9±0.51	0.36	99.9±0.91

***In vitro* dissolution study:** *In vitro* dissolution study was carried out by using USP dissolution 2 apparatus. The release profiles of formulations F1toF15, prepared by using HPMC K4 M, K15 M a K100 M, EC, CAP.

Table.4.*In vitro* drug release study of formulated controlled release tablet

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	40.3± 1.20	36.6± 2.42	32±1. 36	35±1. 20	32.7± 1.36	30.6± 2.38	29±1. 2	26±1. 6	20±0. 43	25± 0.76	26±0. 87	30±0. 45	25± 0.99	26±0. 56	30±0. 84
2	48±2. 31	47.1± 1.20	42.8± 2.54	46±1. 40	41±2. 42	38±1. 54	42±0. 59	36±1. 2	34.1± 0.53	35± 0.98	36±0. 59	34±0. 69	37± 1.54	32±1. 45	38±1. 67
3	59±0. 25	58±0. 20	53.6± 1.56	57.3± 2.20	53±2. 12	46±1. 14	50±0. 45	41±1. 65	41±0. 69	44± 1.18	45.7± 1.44	37±1. 55	46± 1.79	40±1. 86	40±1. 43
4	67±2. 42	66.3± 1.34	61±0. 77	64±0. 10	60.8± 1.34	50.2± 1.10	57±0. 75	50±0. 97	46±1. 23	53± 0.56	54±1. 87	44±1. 98	54± 1.63	47±1. 78	46.4± 1.54
5	76±1. 40	73±1. 10	68±1. 40	72±2. 25	68±1. 20	59±0. 20	62±1. 54	58±0. 58	50±1. 48	62± 0.85	63.3± 1.90	50±0. 97	63± 1.34	54±1. 98	53±1. 98
6	89±1. 10	80±0. 30	74±3. 24	78±1. 26	70±0. 36	64±0. 28	70±1. 48	63±1. 45	55±1. 25	70± 1.17	71±1. 38	58±1. 67	71± 0.56	60±1. 43	60±0. 78
7	98±2. 35	89±2. 62	81±2. 25	84±1. 30	79±0. 28	70±1. 15	75±0. 93	71±1. 22	59±1. 48	75± 1.87	76±1. 06	64±1. 89	76± 0.29	65±1. 38	66±0. 78

8		97±2.10	89±1.15	90±1.38	84±2.56	80±1.64	82±0.45	75±0.67	63±0.45	80±0.99	81±1.54	71±0.98	81±0,88	71±0.57	73±0.98
9			98±0.47	98±0.10	91±1.24	87±2.25	90.2±1.32	83±2.10	70.4±1.82	83±1.57	86±1.39	82±0.43	86±1.43	80±0.65	86±1.26
10					97.8±1.54	94±2.02	97.6±2.05	90±1.28	78±0.96	86±1.54	88±0.82	90±0.84	89±1.68	88±1.43	93±1.42
11						98.8±1.00		98.7±0.62	85±0.76	89	92±0.47	99.1±1.98	91±1.78	94±1.20	99.4±1.38
12									90.2±1.56	92.1	97±0.65		93±1.54	99.7±0.69	

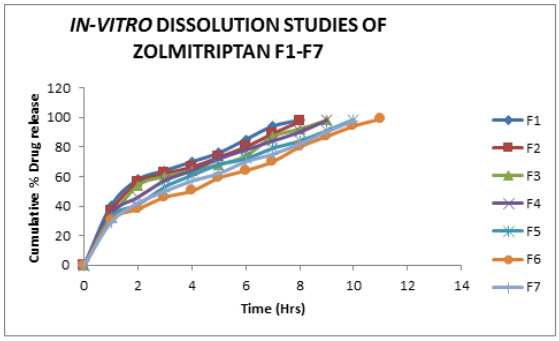

Figure.1.Dissolution profile of prepared formulation F1-F7

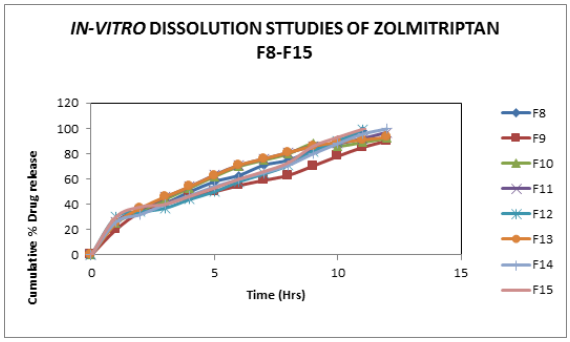

Figure.2.Dissolution profile of prepared formulation F8-F15

In vitro dissolution studies were conducted in 500ml (500ml distilled water + 4.5 ml 0.1 N Hcl) of 0.1 N Hcl buffer using USP-II apparatus at 50 rpm and the temperature of 37±0.50c. Samples of 5ml were collected at different time intervals and analyzed spectrophotometrically at 283 nm. The effect of polymer level on release was studied by varying the levels of HPMC in the matrix tablets. The release pattern of matrix tablet containing 10, 20 and 30% w/w HPMC, K4, K15, K15 with EC and CAP was decipated in Figure. The release rate from F1, F2 and F3 was found to be 98, 97 and 98% at the end of 7^{th}, 18^{th} and 9^{th} hours respectively. Profile of zolmitriptan Hcl from HPMC-K15 matrix formulations F4, F5, and F6 were found to be 98, 97.8 and 98.8% at the end of 9^{th}, 10^{th} and 11^{th} hour respectively. The release profile of Zolmitriptan from HPMC-K100 matrix formulations F7, F8, and F9 were found to be 97.6, 98.7 and 90.2% at the end of 10^{th}, 11^{th}, &12^{th} hour respectively. The release rate decreased as the concentration of HPMC increased which showed that the presence of a highly water-soluble compound, Zolmitriptan, in a HPMC matrix generates an additional osmotic gradient, thereby resulting in a faster rate of polymer swelling and a large increase in gel thickness. In the presence of a solvent, the mobility of the polymer chains is enhanced, resulting in a gradual transformation of a glassy matrix to a rubbery swollen gel. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug. Other factors that may contribute to differences in drug dissolution profile as a function of changes in total polymer concentration include differences in water penetration rate, water absorption capacity and polymer swelling.

As the proportion of HPMC was increased, there was a progressive decline in the release rate because of formation of thick gel structure that delayed the drug release from the matrices, where hydration of HPMC resulted in extensive swelling and increase in the diffusion path length. Swelling studies of HPMC matrices also showed proportionate increase in the swelling with increase in polymer level. However, the results of the in vitro drug release studies indicated that, matrix tablets prepared using HPMC alone could not efficiently control the release of drug even with increased levels of polymers (up to 30%w/w) and thus indicated the need for hydrophobic polymers in the HPMC matrices for controlling the drug release over a period of 12 hours. To assess the influence of hydrophobic polymers in controlling the drug release, six matrix formulations containing combination of HPMC-EC (F10-F12) and with equal proportions were prepared in different polymeric levels like 10, 20 and HPMC-CAP (F13-F15)30% w/w. Similarly, the matrices prepared using combinations of HPMC with EC were subjected for dissolution studies. The release pattern of matrix tablets containing HPMC-EC (F10-F12) is depicted in Fig. 20. The release rate from matrix formulations F7, F8, and F9 was found to be 92.1, 97 and 95% at the end of 12th hours respectively. The release profiles from HPMC-EC formulations showed due more hydrophobic nature of EC. In all the above formulations, delay in drug release was observed due to the presence of hydrophobic polymers like ethyl cellulose and CAP, which restricted the penetration of

dissolution medium inside the matrix and also the formation of gel layer around the matrix.

The observation is further supported by penetration theory, which states that, when a matrix is composed of a water-soluble drug and a water-insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network. As drug release continues, the interconnecting clusters increase the pore network through which interior drug clusters can diffuse with more hydrophobic particles present, and the theory predicts that fewer clusters of soluble drug substance are formed. Furthermore, the presence of finite drug clusters is more statistically plausible. The resulting pore network becomes less extensive and more tortuous resulting in slower drug release. The incorporation of CAP in the matrix not only helped to provide good initial retardation in the release but also helps to enhance the overall release rate of the drug after a suitable lag time. The release profiles showed tri-phasic with initial burst effect (less than 30min) followed by a polymer-controlled slower release in the second phase. The difference in burst effect was the result of difference in the viscosity of the polymers. As it can be seen from polymeric system with low viscosity polymer (HPMC K4 M, K15 M) yielded a faster initial burst effect except HPMC K100 M. There has been considerable interest in using different grades of HPMC in controlled release drug delivery system due to their hydrophilic nature and fast hydration. In conclusion, the matrix tablets prepared with polymeric combination of HPMC-EC and HPMC-CAP showed better controlled release than those prepared using HPMC alone. Among all F1to15 formulation F14 shown better release (99%in 12hours). So F14 formulation which contain HPMC K15 +CAP was selected as optimized formulation.

4. CONCLUSION

From the above study, concluded that F14 was the optimized formulation, among all the formulation F14 formulation containing CAP+HPMC K15M 20% shows that 99% drug release at the end of 12hrs emerging as best formulation which followed by zero order release kinetics Non-Fickian diffusion release.

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