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FORMULATION AND EVALUATION OF MATRIX DIFFUSION DRUG DELIVERY SYSTEM OF TABLETS CONTAINING KETOROLAC BY USING NATURAL POLYMERS

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ABSTARCT

In the present work, an attempt has been made to develop Matrix Diffusion Controlled Release Matrix tablets of Ketorolac by selecting different Types of polymers Aloes Powder, Gum copal, Gum dammar, Neem Resin Powder. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation showed maximum % drug release i.e., 98.39 % in 12 hours hence it is considered as optimized formulation F5 which contains Gum copal (30mg).

KEYWORDS: Ketorolac, Aloes Powder, Gum copal, Gum dammar, Neem Resin, Controlled Release Matrix tablets.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption.[1,2,3] Control release dosage form provides better maintenance of optimal and effective drug level for prolonged duration with less dosing frequency and side effects.[4,5]

Diffusion systems are characterized by release rate of drug is dependent on its diffusion through inert water insoluble membrane barrier. There are basically two types of diffusion devices.[6,7,8]

Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media. The polymers commonly used in such devices are Ethyl cellulose and Poly-vinyl acetate.[9,10]

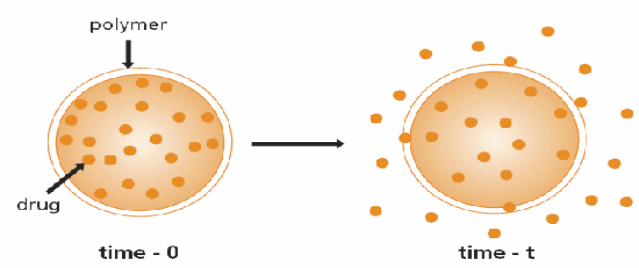

Fig. 1: Schematic Representation of Reservoir.

Diffusion Controlled Drug Delivery Device

A solid drug is homogenously dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.[11]

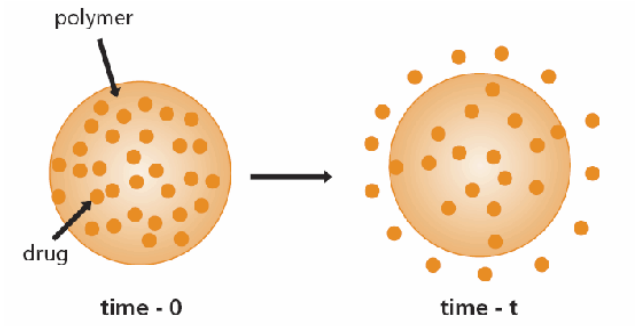

Fig. 2: Schematic Representation of Monolithic (matrix) Diffusion Controlled Drug Delivery Device.

MATERIALS AND METHODS

Materials

Ketorolac was procured from Dr. Reddy's Laboratories (Hyderabad, India). Provided by SURA LABS, Dilsukhnagar, Hyderabad. Aloes Powder, Gum copal, Gum dammar, Neem Resin, Talc was purchased Merck Specialities Pvt Ltd. Lactose was purchased from Strides arcolab, Bangalore, India. Magnesium Stearate was purchased from Hetero labs, Hyderabad.

Methods

Analytical method development

a) Determination of absorption maxima

100mg of Ketorolac pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve

100mg of Ketorolac pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 10,20,30,40 and 50 µg/ml of Ketorolac per ml of solution. The absorbance of the above dilutions was measured at 323 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

***In vitro* drug release studies**

Dissolution parameters

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl, p H 6.8 Phophate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°c $\pm$ 0.5°c

Procedure

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media

was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 323 and 327snm using UV-spectrophotometer.

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Agilent spectrophotometer and the IR spectrum was recorded from 4000cm^{-1} to 500cm^{-1}. The resultant spectrum was compared for any spectrum changes.

Drug Release Kinetics

To analyze the mechanism of drug release from the tablets, the results of in vitro release data were plotted in various kinetic models like zero order, Higuchi model and Korsmeyer-peppas.

RESULTS AND DISCUSSION

Standard Calibration curve of Ketorolac

Table 3: Concentration and absorbance obtained for calibration curve of Ketorolac in 0.1 N hydrochloric acid buffer (pH 1.2).

S. No.	Concentration (µg/ml)	Absorbance (at 323 nm)
1	0	0
2	10	0.127
3	20	0.231
4	30	0.347
5	40	0.461
6	50	0.557

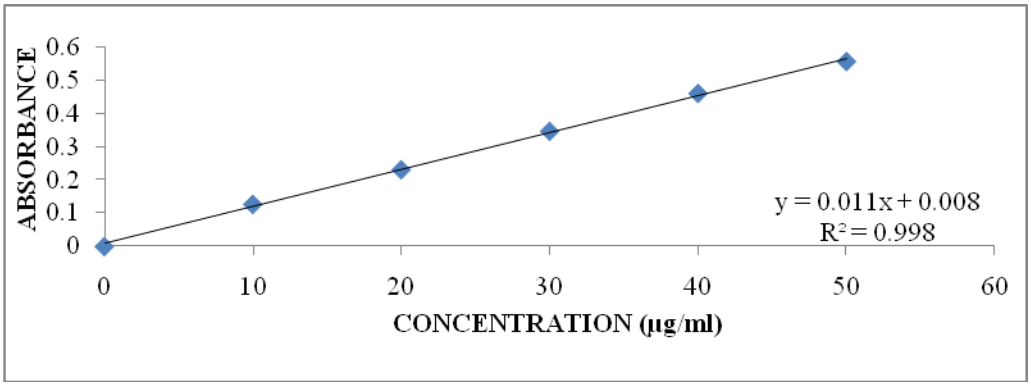

Fig. 3: Standard graph of Ketorolac in 0.1 N HCL.

Table 4: Concentration and absorbance obtained for calibration curve of Ketorolac in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 327 nm)
1	0	0
2	10	0.111
3	20	0.224
4	30	0.314
5	40	0.411
6	50	0.521

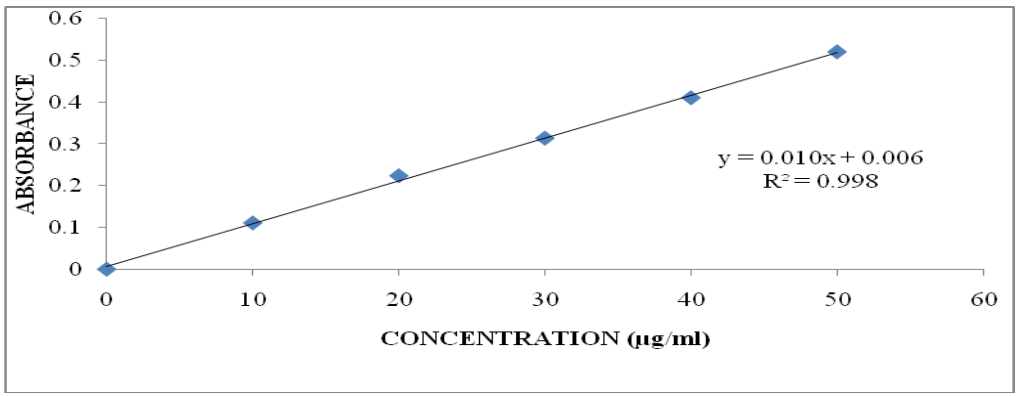

Fig. 4: Standard graph of Ketorolac in pH 6.8 Phosphate buffer.

Evaluation Parameters for sustained release tablets of Ketorolac

1. Pre-compression parameters

Table 5: Pre-compression parameters.

Formulations	Bulk Density(gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose (Θ)
F_1	0.415	0.512	18.94	1.23	32.08
F_2	0.419	0.515	18.64	1.22	30.17
F_3	0.421	0.509	17.28	1.2	29.56
F_4	0.425	0.515	17.47	1.21	31.85
F_5	0.417	0.515	19.02	1.23	29.67
F_6	0.416	0.509	18.27	1.22	32.54
F_7	0.42	0.51	17.64	1.21	31.05
F_8	0.428	0.518	17.37	1.21	30.36
F_9	0.432	0.528	18.18	1.22	30.64
F_{10}	0.43	0.524	17.93	1.21	31.78
F_{11}	0.429	0.518	17.18	1.2	29.08
F_{12}	0.435	0.522	16.66	1.2	32.67

2. Post compression Parameters

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.19 -100.1%.

Table 6: post compression parameter.

Formulations	Average weight (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Assay (%)
F_1	98.12	5.9	3.1	0.19	98.15
F_2	99.36	5.1	3.6	0.47	99.10
F_3	98.15	5.6	3.8	0.34	97.49
F_4	99.10	5.7	3.2	0.66	99.36
F_5	97.96	5.3	3.9	0.57	98.51
F_6	99.25	5.6	3.7	0.12	100.1
F_7	97.48	5.0	3.9	0.26	97.19
F_8	100.1	5.3	3.4	0.38	99.23
F_9	99.56	5.1	3.8	0.22	97.41
F_{10}	98.48	5.7	3.1	0.47	99.87
F_{11}	97.67	5.4	3.7	0.58	98.68
F_{12}	99.79	5.0	3.9	0.61	97.99

3. *In-Vitro* Dissolution studies

In-Vitro dissolution studies were carried out by using 900ml of 0.1 N HCL in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 12 hours. The samples were withdrawn at regular time intervals of 30 min, 1 hour, 2 hr, 3,5,5,6,7,8,9, 10,11 and 12 hours respectively. The results were displayed in table 8.5.

Table 7: *In -vitro* dissolution data.

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	12.19	10.56	9.12	13.96	10.96	13.59	14.61	11.76	8.12	6.02	3.54	2.936
1	19.21	17.61	15.26	25.15	21.56	16.32	21.16	18.71	14.18	10.88	6.77	5.074
2	29.68	23.17	28.10	29.42	33.15	22.11	29.47	22.56	25.40	14.13	10.73	8.326
3	37.49	31.74	39.28	33.98	38.72	29.71	34.15	30.94	36.27	18.46	12.193	11.275
4	43.91	36.84	45.19	36.82	41.18	37.18	42.74	43.59	47.19	34.44	20.82	19.85
5	46.72	42.19	58.93	43.19	47.25	43.78	49.81	49.71	58.70	44.05	37.02	34.10
6	56.46	48.10	62.16	53.92	56.97	52.41	58.27	58.13	65.82	52.90	45.62	45.77
7	59.28	52.74	72.10	58.48	62.98	62.28	69.10	62.95	69.19	74.41	57.11	54.61
8	67.12	65.98	87.93	63.69	68.93	76.90	76.43	68.37	73.59	79.15	69.14	68.06
9	76.73	73.64	94.99	69.87	76.71	84.65	82.91	74.17	80.18	92.61	77.61	73.04
10	82.16	88.92		77.10	86.24	96.72	89.19	82.65	87.36	98.98	87.91	81.25
11	89.47	96.41		89.90	93.70		95.87	87.24	90.41		90.25	86.67
12	94.18			90.12	98.39			90.23	96.25		97.86	91.41

From the tabular column 7 it was evident that the formulations prepared with Aloes Powder as retarding polymer in low concentrations the polymer was produce the required retarding

action to the tablets. As the concentration of polymer increases the retarding nature was decreased. Aloes Powder in the concentration of 15 mg showed good % drug release i.e., 94.18 in 12 hours. Where as in case of formulations prepared with Gum copal as retarding polymer, the formulations with 30 mg concentration of polymer showed complete drug release in 12 hours. whereas the concentration of polymer increases the retarding nature also increased. The Formulation Containing Gum copal in 30 Mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.39%. Where as in case formulations prepared with Gum dammar as retarding polymer, as the concentration of polymer increases the good drug release nature was also increased. Where as in case formulations prepared with Neem Resin as retarding polymer, as the concentration of polymer increases the retarding nature was also decreased.

All the Formuations are not fallows desired drug release upto 12 hours. Only some concentrations only release the drug release upto 12 hours. From the above results it was evident that the formulation F5 is best formulation with desired drug release pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release mode.

Table 8: Release kinetics data for optimised formulation FTIR.

Cumulative (%) Release Q	Time (T)	Root (T)	Log (%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release / t)	1/Cum% Release	Peppas log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
10.96	**0.5**	0.707	1.040	-0.301	1.950	21.920	0.0912	-0.960	89.04	4.642	4.465	0.176
21.56	**1**	1.000	1.334	0.000	1.895	21.560	0.0464	-0.666	78.44	4.642	4.281	0.361
33.15	**2**	1.414	1.520	0.301	1.825	16.575	0.0302	-0.480	66.85	4.642	4.059	0.583
38.72	**3**	1.732	1.588	0.477	1.787	12.907	0.0258	-0.412	61.28	4.642	3.943	0.699
41.18	**4**	2.000	1.615	0.602	1.770	10.295	0.0243	-0.385	58.82	4.642	3.889	0.753
47.25	**5**	2.236	1.674	0.699	1.722	9.450	0.0212	-0.326	52.75	4.642	3.750	0.891
56.97	**6**	2.449	1.756	0.778	1.634	9.495	0.0176	-0.244	43.03	4.642	3.504	1.137
62.98	**7**	2.646	1.799	0.845	1.568	8.997	0.0159	-0.201	37.02	4.642	3.333	1.309
68.93	**8**	2.828	1.838	0.903	1.492	8.616	0.0145	-0.162	31.07	4.642	3.144	1.498
76.71	**9**	3.000	1.885	0.954	1.367	8.523	0.0130	-0.115	23.29	4.642	2.856	1.786
86.24	**10**	3.162	1.936	1.000	1.139	8.624	0.0116	-0.064	13.76	4.642	2.396	2.245
93.7	**11**	3.317	1.972	1.041	0.799	8.518	0.0107	-0.028	6.3	4.642	1.847	2.795
98.39	**12**	3.464	1.993	1.079	0.207	8.199	0.0102	-0.007	1.61	4.642	1.172	3.470

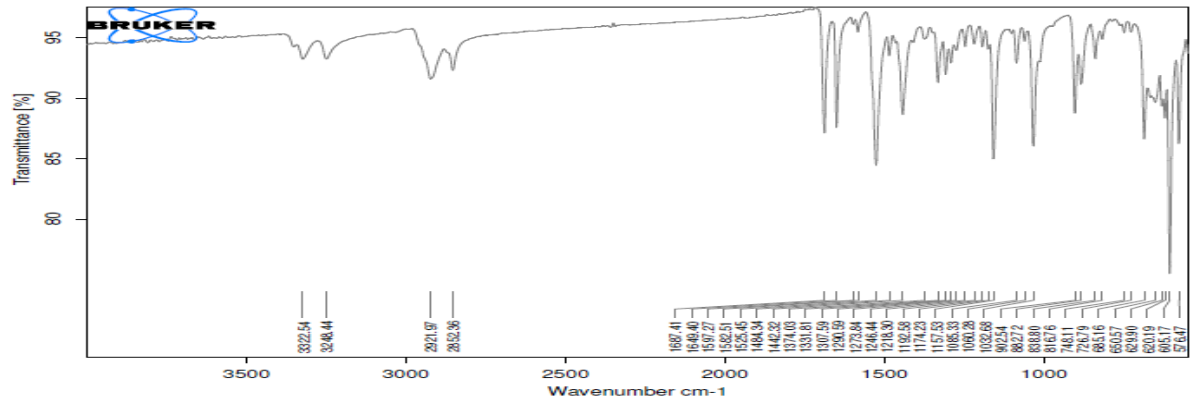

Fig. 14: FT-IR Spectrum of Optimised Formulation.

There is no incompatibility of pure drug and excipients. There is no disappearence of peaks of pure drug and in optimised formulation.

CONCLUSION

In the present work, an attempt has been made to develop Matrix Diffusion Controlled Release tablets of Ketorolac by selecting different Types of polymers. Aloes Powder, Gum copal, Gum dammar, Neem Resin as retarding. All the formulations were prepared by direct compression method. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation showed maximum % drug release i.e., 98.39% in 12 hours hence it is considered as optimized formulation F5 which contains Gum copal (30mg).

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REFERENCES

1. Sathish Ummadi, B. Shravani, N. G. Raghavendra Rao, M. Srikanth Reddy, B. Sanjeev Nayak. Overview on Controlled Release Dosage Form. International Journal of Pharma Sciences, 2013; 3(4): 258-269.

2. Brahmankar D.M. and Jaiswal S.B. “Biopharmaceutics and Pharmacokinetics” a Treatise. Vallabh Prakashan, First Edition, 1995; 336-337.
3. Lachman Leon, Lieberman Herbert A., Kanig Joseph L. “The theory and practice of industrial pharmacy” Second edition, Varghese publishing house; Bombay, 1996; 171-196.
4. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics: Pharmacokinetics. 2nd ed. Vallabh Prakashan, Delhi, 2009; 399-401.
5. John C, Morten C, The Science of Dosage Form Design, Aulton: Modified release peroral dosage forms. 2nd ed. Churchill Livingstone, 2002; 290-300.
6. Ali Nokhodchi, Shaista Raja, Pryia Patel, and Kofi Asare-Addo. The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems. Bioimpacts, 2012; 2(4): 175–187.
7. John C, Morten C, The Science of Dosage Form Design, Aulton: Modified release peroral dosage forms. 2nd ed. Churchill Livingstone, 2002; 290-300.
8. Sathish Ummadi, B. Shravani, N. G. Raghavendra Rao, M. Srikanth Reddy, B. Sanjeev Nayak. Overview on Controlled Release Dosage Form. International Journal of Pharma Sciences, 2013; 3(4): 258-269.
9. Vyas S, P, Khar RK.Controlled Drug delivery: Concepts and Advances .Concepts and Advances. 1st ed. vallabh prakashan, 2002; 156-189.
10. Shargel L, Yu ABC. Modified release drug products. In: Applied Biopharmaceutics and Pharmacokinetics. 4th ed. McGraw Hill, 1999; 169-171.
11. Welling P. G. and Dobrinska M. R., Dosing consideration and bioavailability assessment of controlled drug delivery system, Chapter 7, Controlled drug delivery; fundamentals and applications, 2nd edition, Robinson J.R. and Lee V. H. L. (Eds.), Marcel Dekker Inc., New York, 1978; 29: 254, 373.
12. Manisha Gahlyan, Saroj Jain. Oral Controlled Release Drug Delivery System- A Review.
13. Mamidala R, Ramana V, Lingam M, Gannu R, Rao MY. Review article factors influencing the design and performance of oral sustained/controlled release dosage form. Int. journal of pharmaceutical science and nanotechnology, 2009; 2: 583.
14. Patel Nidh, Chaudhary Anamika, Soni Twinkle, Sambyal Mehul, Jain Hitesh, Upadhyay Umesh. Controlled Drug Delivery System: A Review. IAJPS, 2016; 3(3): 227-233.
15. Crank, J. The Mathematics of Diffusion. New York: Oxford Press, 1975.
16. Leon, L., & Herbert, L.A. Pharmaceutical Dosage Forms. New York: Marcel Dekker, 2002.

17. Kar RK, Mohapatra S and Barik BB. Design and characterization of controlled release matrix tablets of Zidovudine. Asian J Pharm Cli Res, 2009; 2: 54.
18. Salsa T, Veiga F and Pina ME. Oral controlled release dosage form. I. Cellulose ether polymers in hydrophilic matrices. Drug Develop Ind Pharm, 1997; 23: 929-938.
19. Kumar S, Shashikant and Bharat P. Sustained release drug delivery system: a review. Int J Inst Pharm Life Sci., 2012; 2(3): 356-376.
20. Cristina M, Aranzaz; u Z and Jose ML. Critical factors in the release of drugs from sustained release hydrophilic matrices. J Control Rel., 2011; 154: 2-19.