ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Studies on formulation and development of oxybutynin chloride matrix tablet for oral extended release therapy and *In-vitro* evaluation

Raslamol K*, Saraswathi R, Subash S Pillai, Dilip C, Sankar C, Krishnan PN

Al Shifa College Of Pharmacy, Kizhattur, Perinthalmanna, Kerala.Pin-679325, India.

ABSTRACT

Formulation and Development of Monolithic Oxybutynin chloride tablet would offer advantages of lesser anticholinergic side effect, reduce the first pass metabolism , overcome the bioavailability problems, improve patient compliance and due to well controlled drug release in the intestinal tract it avoids the dose dumping phenomenon and the release of drug can be achieved over a period of 16 hours. Matrix tablets were prepared using Oxybutynin chloride, different concentrations of polymers (HPMC, EC, PVP, METHOCEL K 100), excipients, lubricants, calcium replenisher and viscosity enhancers using wet granulation technique to contain 5 mg of Oxybutynin chloride .Formulations prepared were evaluated for the release of Oxybutynin chloride over a period of 16 hours. First two hours in Phosphate buffer with pH 1.2and remaining 14 hours in pH 6.8 phosphate buffer using United States Pharmacopeia (USP) type II dissolution apparatus. Along with usual physical properties, the swelling and erosion studies of tablet were also investigated. The in vitro drug release study revealed that HPMC K100 ER at a concentration of 8.5% and higher concentration of diluent (lactose) of the dosage form was able to control the simultaneous release of Oxybutynin chloride for 16 hours. The release of best formulation trial matched with the commercial ER tablet of Oxybutynin chloride with kinetic models. Water uptake and erosion study of tablets indicated that swelling followed by erosion could be the mechanism of drug release. The in vitro release data of formulation trial (A 15) and commercial ER tablet (CF) followed Korsmeyer-Peppas and zero-order kinetics, respectively. In conclusion, the in vitro release profile and the mathematical models indicate that release of drug from matrix tablet can be effectively controlled from a single tablet using polymer as mythical K 100.

Key words: .oxybutynin chloride (OXB), Extended Release (ER), Commercial Formulation (CF)

Corresponding author
E-mail: raslamolk@gmail.com

ISSN: 0975-8585

INTRODUCTION

Oxybutynin chloride is a safe and effective drug for the treatment of urinary incontinence due to bladder disfunction [1].Development of Monolithic Oxybutynin chloride tablet formulation would offer advantages of lesser anti cholinergic side effect, due to well controlled drug release in the intestinal tract, it avoids the dose dumping phenomenon and the release of drug can be achieved over a period of 16 hours. The most established antispasmodics must be taken several times a day thus Extended release (ER)formulations of oxybutynin chloride antispasmodics have been developed to reduce dose frequency and to maintain constant plasma drug concentration and to reduce adverse effects. Economy and greater patient compliance are other advantages. Extended release can be achieved by formulating drugs as matrix devises using different sellable polymers. The monolithic Oxybutynin chloride matrix tablet formulation comprises the drug, water sellable polymers, lactose, lubricants, calciumchloride, sodium alginate and magnesium separate. Extended release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects [2].Economy and greater patient compliance are other advantages. Combination of sodium alginate, cetostearyl alcohol, Methocel K 100 as the polymer matrix resulted zero-order release. Matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behavior [3].Oxybutynin chloride is an anti cholinergic medication used to relieve urinary and bladder difficulties, including frequent urination and inability to control urination, by decreasing muscle spasms of the bladder. It competitively antagonizes the M1, M2, and M3 subtypes of the muscarinic acetylcholine receptor. Oxybutynin chloride is an antispasmodic, anti cholinergic agent. The mechanism of action of Oxybutynin chloride was, it exerts direct antispasmodic effect on smooth muscle and inhibits the action of acetylcholine at postganglionic cholinergic sites, thus increasing bladder capacity and delaying the initial desire to void by reducing the number of motor impulses reaching the depressor muscle. It does not block acetylcholine effects at skeletal myoneural junctions nor at autonomic ganglia; neither does it have effect on the smooth muscle of blood vessels. [4] So, the objective of the present study was to develop controlled and extended release formulation of Oxybutynin chloride as matrix tablets. The drug release rates from matrix tablets were compared with marketed ER formulation. Matrix erosion and swelling studies were also carried out by slightly modified method (Munsday and Cox, 2000) [5]. The release kinetics and mechanism of drug release by regression coefficient analysis and Peppas exponential release model equation i.e. $Mt/M\infty = Ktn$ were also investigated.

MATERIALS AND METHOD

Oxybutynin Chloride and polymers Methocel K100, PVP were obtained as gift sample from Zydus Cadila healthcare Ltd, Mumbai and EC and HPMC were as gift sample from Modern pharmaceuticals Pvt Ltd, Tirur. .All chemicals and reagents used throughout the study were of analytical grade.

Preparation of Tablet

Ingredients per tablet(in mg) are given in TABLE NO:1.All the batches of matrix tablets were prepared using 40mg of Na alginate, 40mg of Ceto stearyl alcohol, 6mg of Calcium chloride and 2mg of Mg stearate. The variables in batches were the type of polymers and quantity of drug and quantity of excipients .Each batch size of tablet was 100.All the ingredients were passed through sieve No.60,and the amount(required to prepare a 100 tablet batch) of the drug, polymer(ethyl cellulose, hydroxy propyl methyl cellulose, Poly Vinyl Pyrolidone ,Methocel K 100),excipient (Lactose),calcium replenisher (Calcium chloride) and edible hydro carbon (Ceto stearyl alcohol)was mixed thoroughly. A sufficient volume of the specified granulating agent was added slowly. After enough cohesiveness was obtained, the mass was sieved portion wise through sieve No.16.The granules were dried at temperature of 72º F (22.2ºC) until moister content reached less than 0.5% w/w[5]. The dried granules were collected and screened through sieve No.20 & 2% w/w magnesium stearate was added as lubricant and then compressed using single punch tabletting machine. All compressed tablets were stored in an airtight container at room temperature for further studies.

Evaluation of Tablets

The prepared tablets were tested as per standard procedure for weight variation (n = 20), hardness (n = 6), thickness (n = 20), diameter, friability, water uptake, and erosion characteristics. Hardness of tablet was determined by using a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). Friability test (n = 20) was conducted using Roche friabilator (Electrolab EF-2(USP). Thickness of the tablets was measured by digital Vernier caliper (Mitutoyo Corp, Kawasaki, Japan). Drug content of Oxybutynin Chloride was analyzed by measuring the absorbance of standard and samples at λ = 344nm using UV/Visible spectrophotometer (Schimadzu).

Swelling and erosion studies

The matrix tablets swelling and erosion studies were carried out by following slightly modified method (Munsday and Cox, 2000) [6].The studies were done using the USP xxIV Dissolution apparatus 1 fitted with six rotating baskets. (model electrolab ,India).All the batches of tablets were evaluated (3 runs for each batch)using 500ml dissolution medium at P^H 1.2 for first two hours and p H 6.8 was used for remaining 14 hours. Temperature maintained at 37±0.1ºC and stirred at 100rpm.Each basket was thoroughly cleaned, accurately weighed before and after insertion of a matrix tablet, so that accurate weight of each matrix tablet (W1) could be calculated .The baskets and tablets were then rotated in the dissolution medium, at regular time intervals a basket was detached, blotted with absorbent paper to remove any excess medium on the basket surface and accurately weighed on analytical balance. From these hydrated matrix ,tablet weight (Wh) was calculated.Then the hydrated matrices were dried in an oven at 40ºC for 18 hours, cooled in a desiccators(silica gel) and dried residue weighed.The heating- cooling- weighing process was repeated until

constant weight (Wd) was achieved. At the time of detachment of each basket, 5 ml samples of dissolution medium were withdrawn and an equivalent volume of medium at 37ºC was added to maintain constant volume.Withdrawn samples were analysed spectrometrically at 344nm using UV spectrophotometer. This gave the amount of drug released (Qt) from tablets at time t.Percentage swelling and erosion of matrix tablet after dissolution at time't' was calculated as follows: (Munsday and Cox, 2000).

$$\% \text{ Matrix Swelling} = \{(Wh + Qt) - Wi\} / Wi * 100$$
$$\% \text{ Matrix Erosion} = (Wi - Wd - Qt) / Wi * 100$$

Where, Wi = initial tablet matrix weight
Wh = Hydrated matrix tablet weight after time t
Wd = Dried matrix weight after time t
Qt = Amount of drug released at time t

In Vitro Drug Release Characteristics

Release rate of all the designed formulations were studied up to 16 hours using USP-22 type 2 dissolution apparatus at 100 rpm. 900 milliliters of phosphate buffer at p H 1.2 was used for first two hours and PH 6.8 was used for remaining 14 hours. Temperature maintained at 37°C ± 0.5°C. At each predetermined time points (.5, 1, 1.5, 2, 4, 8, 12, 16minutes), 20 milliliters of the sample was withdrawn at regular intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No. 1, Whatman, Maidstone, UK) samples were analysed by UV (at 344 nm) spectrophotometric method[7].

The suitability of several equations, which have been reported in the literature to define drug release mechanism(s), was tested with respect to the release data. To analyze the mechanism of drug release from the matrix tablets, data obtained from the drug release studies were analyzed according to Equations 3, 4, and 5 of the zero-order model,first order,Higuchi model, and the Korsmeyer-Peppas model[8], respectively:

$$C = K_0 t \quad \ldots\ldots 1$$
$$\text{Log } C = \text{Log } C_0 - k t / 2.3032 \quad \ldots\ldots 2$$
$$Q = K_H t^{1/2} \quad \ldots\ldots 3$$
$$Mt/M\infty = Ktn \quad \ldots\ldots 4$$

In all mathematical expressions, K_0 is the zero-order rate constant, t is the time in hours, C0 is the initial concentration of drug, k is the first order constant, Mt/M is the fractional solute release, K is a kinetic constant characteristic of the drug / polymer system K_H is the Higuchi rate constant, and n is the release exponent, which characterizes the mechanism of drug release.

RESULTS AND DISCUSSION

ISSN: 0975-8585

The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in the body. So that the desired drug concentration can be achieved promptly and they are maintained. The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds. Hydrophilic polymer matrix system are widely used in the oral controlled drug delivery because they make it easier to achieve a desirable drug release profile, they are cost effective and they have broad US food and drug administration acceptance. The hydrophilic matrix system consists of hydrophilic polymer, drug and other excipinets distributed throughout the matrix.

This dynamic system is dependent on polymer wetting, hydration and dissolution for controlled release of drug. At the same time other soluble exipients or drug substance will also wet, dissolve, and diffuse out of the matrix, whereas insoluble exipients or drug substance will be held in place until the surrounding polymer, exipients or drug complex erodes or dissolves away. By using four different hydrophilic polymers such as Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose or Poly Vinyl Pyrolidone or Methocel K 100 were tried for the formulation of ER of Oxybutynin chloride. The extended release tablet was formulated by wet granulation technique. The oxybutanin chloride, extended release polymers, solubilizing agent, diluents are passed through sieve no.24.With proper blending these materials are kept for dry mixing which leads to the formation for uniform matrix system. Aqueous system is for the formation of granules such as sodium alginate in water act as a binder, which leads to the formations of granules. After that the wet screening that wet mass, granules kept for drying in the dehumidifier environment for sufficient time. After that lubrication done with the help of magnesium stearate and talc, then granules are ready for compression and compression are done with the help of tablet compression machine by using a punch size of 10 mm, CPL embossing on one side along with scored line on another side.

Physical Properties

The results of the uniformity of weight, hardness, diameter and thickness, and friability of the tablets are given in TABLE NO: 2.All the samples of the test product complied with the official requirements of uniformity of weight. The friability test was done using Roche Friabilator reveals that the friability were within the range of 0.01% and 0.45%.As the polymer concentration increases then the friability also increased. The hardness of the tablets were done using the “Monsanto tester” it reveals that the hardness were within the range of 4 Kg/cm^2 to 6Kg/cm^2. The diameter and thickness of the tablets were found to vary in narrow limit for all formulations. If the polymer concentration increases then the thickness of the tablet also increased [9].

Swelling and erosion studies

Since the rate of swelling and erosion is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and the erosion of the hydrated tablets were determined. Simultaneously with the liquid uptake study, the degree of

ISSN: 0975-8585

Table 1: INGREDIENTS PER TABLET(in mg)

Batch code	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16
Drug (Oxybutinin chloride)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Polymer used	HPMC	HPMC	HPMC	HPMC	EC	EC	EC	EC	PVP	PVP	PVP	PVP	Methocel K 100	Methocel K 100	Methocel K 100	Methocel K 100
Quantity of polymer	25	35	45	55	25	35	45	55	25	35	45	55	25	35	45	55
Sodium alginate	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Lactose	282	262	272	252	282	262	272	252	282	262	272	252	282	262	272	252
Ceto stearyl alcohol	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Calcium chloride	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Final weight of tablet	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400

polymer erosion was measured.The percentage matrix swelling and erosion of tablet at various time intervals is shown in (GRAPH NO:1 & 2).Erosion study of 16 batches showed that matrix erosion decreased with increase in polymer concentration .The formulation trial A 15 shows best matrix swelling property compared to other batches (GRAPH NO:3) and matrix erosion of formulation trial A 15 formulation trial is 37.86(GRAPH NO:4).A 11 shows maximum erosion(43.96).it is clear that the matrices underwent both swelling and erosion[9] at the same time after placement in the dissolution media. Since both swelling and erosion occurred simultaneously in the matrix, constant release can be obtained in these matrices .constant release from such formulations occurs because of increase in diffusion path length due to swelling is compensated by continuous erosion of the matrix [10].

ISSN: 0975-8585

TABLE NO: 2 Average weight, % friability, Hardness, thickness and diameter of the prepared matrix tablets, Expressed as Mean ± SD

Batch code	Average weight of tablet in mg	% friability	Hardness(Kg/cm²)	Average tablet thickness in mm	Average tablet diameter in mm
A 1	405.19 ± 3.2	0.01	4.45 ± 0.02	3.01 ± 0.04	8.98 ± 0.01
A2	403.87 ± 2.1	0.45	4.30 ± 0.01	2.99 ± 0.03	8.99 ± 0.02
A3	406.53±4.1	0.13	4.22 ± 0.05	3.00 ± 0.01	8.97 ± 0.01
A4	404.85±3.5	0.24	4.25 ± 0.02	3.02 ± 0.03	9.00 ± 0.00
A5	404.04±2.6	0.03	4.24 ± 0.04	3.00 ± 0.02	8.98 ± 0.03
A6	407.46±1.9	0.11	4.31 ± 0.01	2.98 ± 0.02	9.01 ± 0.02
A7	402.01±2.4	0.08	4.45 ± 0.02	2.99 ± 0.01	9.02 ± 0.01
A8	404.55±3.3	0.05	4.26 ± 0.03	2.97 ± 0.03	8.97 ± 0.03
A9	403.93±1.4	0.05	4.25 ± 0.02	3.00 ± 0.02	8.99 ± 0.01
A10	405.30±3.2	0.12	4.34 ± 0.01	3.01 ± 0.01	9.01 ± 0.01
A11	408.98±2.2	0.07	4.46 ± 0.05	3.05 ± 0.04	9.00 ± 000
A12	403.02±2.5	0.04	4.40 ± 0.11	3.00 ± 0.03	9.02 ± 0.03
A13	404.03±1.3	0.06	5.25 ± 0.03	3.04 ± 0.01	9.01 ± 0.02
A14	403.99±2.0	0.09	5.31 ± 0.05	3.06 ± 0.03	9.00 ± 0.00
A15	405.79±3.2	0.04	5.36 ± 0.02	3.05 ± 0.02	9.02 ± 0.01
A16	407.89±1.8	0.16	5.21 ± 0.14	3.01 ± 0.04	9.00 ± 0.00

ISSN: 0975-8585

TABLE NO: 4 showing the drug release data's for all formulation trials

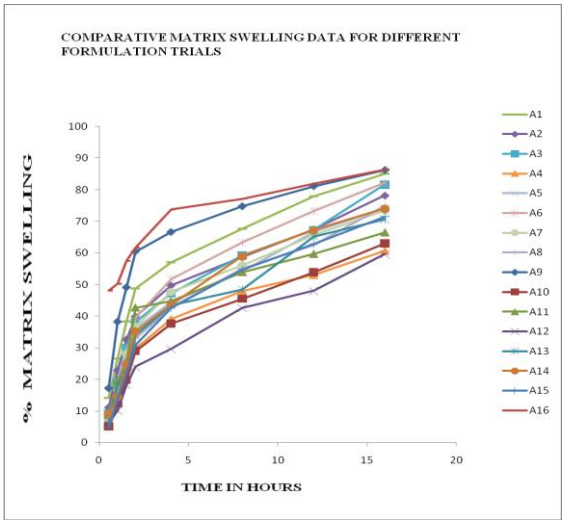
Batch code	Time for maximum release	%Cumulative release
A1	16	78.73
A2	16	80.79
A3	16	77.55
A4	16	71.24
A5	16	80.20
A6	16	78.22
A7	16	80.48
A8	16	78.68
A9	16	78.80
A10	16	76.90
A11	16	78.22
A12	16	76.87
A13	16	86.25
A14	16	85.50
A15	16	88.71
A16	16	81.07
CF	16	85.69

ISSN: 0975-8585

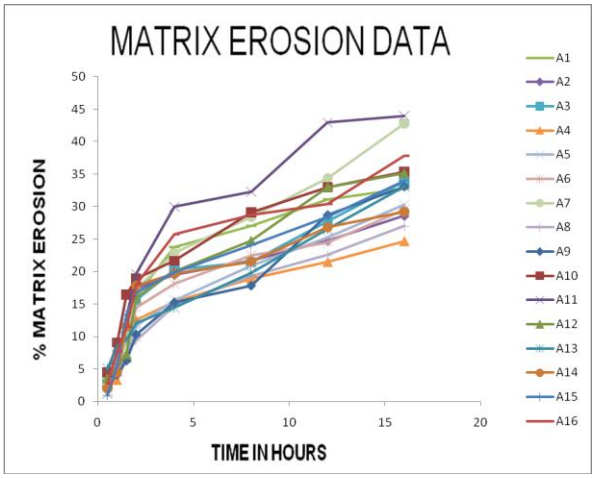
TABLE NO: 3 showing the swelling and erosion data's for formulation trial No.A15

Time in hours	Weight of hydrated matrix(mg)	% Matrix swelling	Weight of eroded matrix(mg)	% Matrix erosion
0.5	606.30	48.11	396.31	2.78
1	612.22	50.34	372.73	7.71
1.5	635.74	57.47	351.25	11.49
2	647.00	61.74	317.86	18.04
4	692.10	73.76	279.69	25.79
8	698.31	77.15	261.44	28.75
12	712.77	81.83	253.17	30.43
16	724.68	86.34	245.22	37.86

GRAPH NO: 1 showing graph for % matrix swelling for all formulation trials

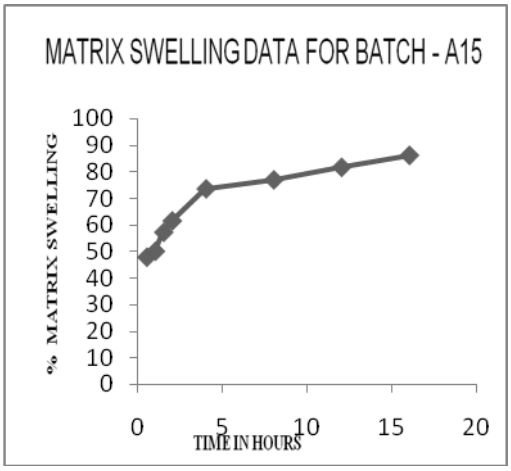


GRAPH NO: 2 showing graph for % matrix erosion for all formulation trials

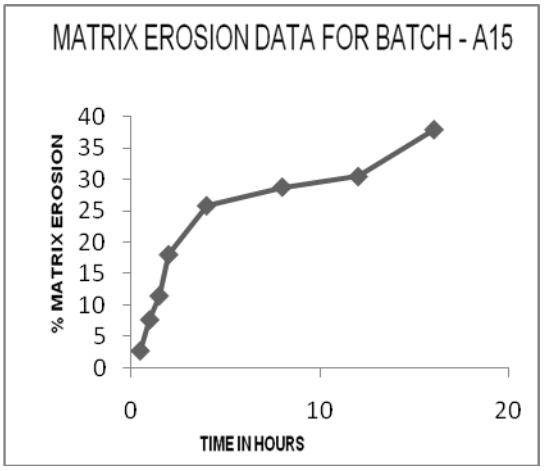


ISSN: 0975-8585

MATRIX SWELLING AND EROSION DATA FOR FORMULATION TRIAL A15
(Best formulation)



GRAPH NO: 3 showing graph for % matrix swelling



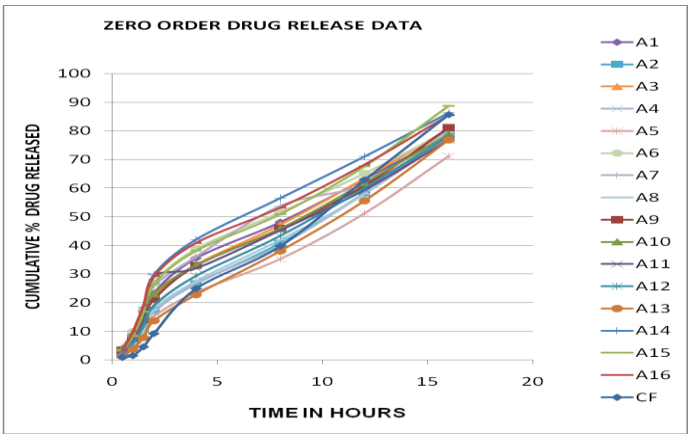
GRAPH NO: 4 showing graph for %matrix erosion

In Vitro Release Studies

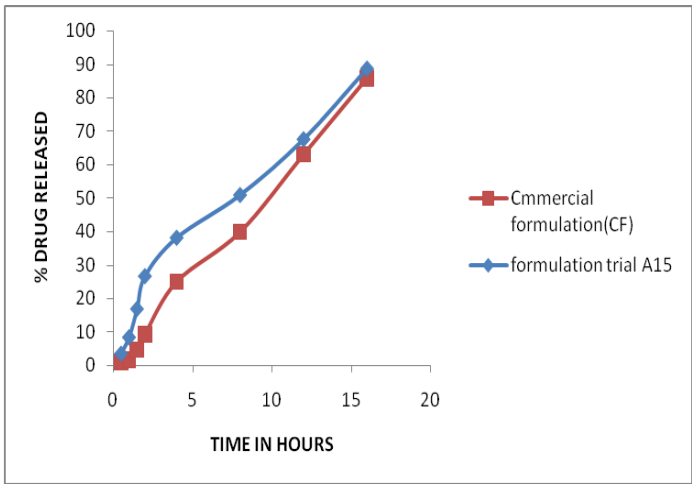
In present work, formulation trial A1 to A4 was taken with the help of Extended Release (ER) polymer of Hydroxy Propyl Methyl cellulose, formulation trial A5 to A8 was taken with the help of Extended Release (ER) polymer Ethyl cellulose, formulation trial A9 to A12was taken with the help of Extended Release (ER) polymer Poly Vinyl Pyrrolidone and formulation trail A13 to A16 was taken with the help of Extended Release (ER) polymer Methocel K 100 .In A1-A4 % cumulative drug released (78.73, 80.79, 77.55,71.24) was less than the commercial formulation. And in A5- A8 % cumulative drug released (80.20, 78.22, 80.48, 78.68) was less than the commercial formulation And by comparing F1 to F4 % drug released of oxybutynin chloride was increased with the help of ethyl cellulose and lactose act as a channelizing agent but it in presence of lactose, lead to produce a discoloration of tablet and chances of drug instability is more. By comparing the formulation trial A9 to A12, the % drug release at the end of 16hr was very less(78.80, 76.90, 78.22, 76.87).From these 4 formulation trials, it is concluded that PVP was not suitable Extended Release (ER) polymer for the development of matrix tablet of oxybutynin chloride. In A13- A16 % cumulative drug release is more than the previous 12 formulation trials. From these A13, A14, A15 AND A16 (METHOCEL K 100 formulation trials) the release was 86.255%, 85.5%, 88.71% and 81.07 % at the end of 16th hour. The release from commercial formulation was 85.69% at the end of 16th hour. By observing all 4 previous formulation trial it is concluded that in the presence of METHOCEL K 100 it is possible to get good In-vitro dissolution data in the case of formulation trials A15 shows more release compared to the commercial formulation (GRAPH NO: 6). So formulation trial A15 is considered as the best formulation and METHOCEL K 100 is considered as good extended releasing agent compared to HPMC E464, EC and PVP. GRAPH NO: 5 showing the drug release data's for all formulation trials. In vitro studies indicated that the rate and extent of drug release were decreased significantly with an increase in polymer concentration, which may be attributed to

ISSN: 0975-8585

GRAPH NO: 5 showing the drug release data's for all formulation trials.



GRAPH NO: 6 Comparative in vitro release profile for commercial formulation (CF) and Best formulation trial A15.



increase in the density of polymer matrix followed by increasing diffusional path length for drug molecules [11].

Identification of the Mechanism by Which the Drug Is Released

On the In-vitro dissolution study of the commercial formulation, the data was fitted in various kinetics models such as zero order, first order, Korsmeyer –peppas, Higuchi-model of drug release on the basis of best fit with highest correlation (r^2), from these studies it is concluded that ,in the optimized formulation trial No.A15 follows Zero order and which correlates with the commercial formulation. Based on various mathematical models, the magnitude of the release exponent "n" indicates the release mechanism (ie, Fickian diffusion, case II transport, or anomalous transport). In the present study, the limits considered were n = 0.45 (indicates a classical Fickian diffusion-controlled drug release) and n = 0.89 (indicates a case II relaxational release transport; non-Fickian, zero-order release). Values of n between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated

matrix and the polymer relaxation) commonly called anomalous transport [12]. In the case of best formulation trial A15and commercial formulation (CF) the n value was equal to 0.858(A15) and 0.839(CF). According to kosmeyer-peppas kinetic model, If n 0.45<0.89 indicates anomalous diffusion or non-fickian diffusion. Anomalous diffusion or non-fickian diffusion refers to combination of both diffusion and erosion controlled rate release.

CONCLUSION

Results of the present study demonstrate that the formulation trial A 15 containing 45mg of METHOCEL K 100 and 5mg of oxybutynin chloride was found to release the drug the maximum of 88.71% in zero order kinetics. It is evident that the investigated controlled release matrix methocel K 100 was capable of prolonging the release of drug simultaneously for 16 hours. The mechanism of drug release was observed to be following Korsmeyer-Peppas model and zero-order kinetics for formulation trial A 15 and commercial formulation respectively.

ACKNOWLEDGEMENTS

The authors thank Mr. P. Unneen, Managing Trustee, Shifa Medicare Trust, Perinthalmanna, for the encouragement and support provided.

REFERENCES

[1] IMS America. 1999. National Prescription Audit Plus Database, Plymouth Meeting, PA
[2] Shargel L, Yu ABC. Modified release drug products. In: Applied Biopharmaceutics and Pharmacokinetics. 4th ed. McGraw Hill. 1999; 521-522.
[3] Mishra B, Seena J, Singh S, Sankar C. Indian Pharm 2003;2:86-89. .Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Int J Pharm 1983; 15:25–35.
[4] Ditropan package insert (Marion Merrell Dow—US), 1992 PDR. McEvoy G, editor. AHFS Drug Information. Bethesda, MD: American Society of Hospital Pharmacists 1990: 2096-8.
[5] United States Patent Application 20080299207 provides data about,"Methods and compositions for administration of oxybutynin description/claims, U.S. Provisional Application Ser. No. 60/940,907, filed May 30, 2007
[6] Munday DL, Cox PJ. Int J Pharm 2000; 203:179-182.
[7] Manthena VS, Varma Aditya, M Kaushal, Sanjay Garg. J Pharm Biomed Anal 2004;36: 669–674.
[8] Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Int J Pharm 1983; 15:25–35.
[9] Hamdy Abdelkader, Ossama Youssef Abdalla, and Hesham Sale. AAPS PharmSciTech 2008;9(2):675-683
[10] J Sujja-areevath, DL Munday, PJ Cox and KA Khan. Eur J Pharm Sci 1998;6(1): 207-217.
[11] Sankar C, Rani M, Srivastava AK, Mishra B. Pharmazie 2001; 56: 223-226.
[12] Mario Grassi, and Gabriele Grassi. Curr Drug Del 2005; 2(1): 97-116.