International Journal of Farmacia

Journal Home page: www.ijfjournal.com

Formulation and evaluation of sustained release tablets of gemifloxacin using natural polymers

S.Kavibharathi, S.Chandra, R.Veerajothi, S.Sangeetha, N.Senthil Kumar, R.Suresh

JKKMRF'S ANNAI JKK SAMPOORANI AMMAL COLLEGE OF PHARMACY - Komarapalayam

ABSTRACT

Extended-release drug-delivery systems are designed to release drugs over a prolonged period employing steady-rate drug release or controlled release to achieve stable and higher therapeutic potential while minimizing adverse side effects. Sustain release tablets of gemifloxacin were prepared by using polymer Xanthan gum, guar gum, carbopol 937 in all formulation. The ingredients given in table, except glidant and lubricant were thoroughly mixed in mortar and pestle. The wet mass passed through sieve no.16 and c for 30-45. The present work to aim the design, fabrication and evaluation of Gemifloxacin sustained release tablets by wet granulation technique. In this technique Guar Gum and Xanthan Gum were used as polymers for drug released upto extended time period. The Formulations F6 found to satisfy the desired criteria for GFX released from the formulation. The drugs released from the formulations and released mechanism followed for "first order kinetics & Non-Fickian diffusion mechanism" respectively. Finally to achieve a Gemifloxacin sustained released tablets and drugs released up to 12 hrs. The Comparison of the optimized formulation (F6) with market formulation (FM).

Keywords: Sustained release, Gemifloxacin, natural polymers, Guar Gum, Xanthan Gum

INTRODUCTION

Gemifloxacin Mesylate is a new fluoroquinolone antibacterial agent with a broad spectrum of activity. It is a fourth generation fluoroquinolone, has high potency against Gram-positive, Gram-negative bacteria and its bactericidal activity is through inhibition of bacterial topoisomerase II and IV enzymes which are critical in the maintenance, synthesis and replication of DNA. Gemifloxacin mesylate showed good in vivo activity in a model of infective keratitis due to St. aureus, in comparison to all third generation fluoroquinolones. It is freely soluble in water. Bioavailability is approximately 71 %. The half-life of drug is low that is 7 h. The purpose of the present investigation is to develop a sustained release, ophthalmic delivery system of Gemifloxacin Mesylate with more residence time in the eye which leads to improvement of bioavailability, patient compliance and to reduce the frequency of administration. The conventional liquid ophthalmic formulations are washed out from the precorneal area immediately upon instillation because of constant lacrimal secretion, nasolacrimal drainage and short precorneal residence time of the solution. Narrow permeability of the cornea contributes to the low absorption of ocular drugs. Rapid elimination of the eye drops administered often results in a short duration of the therapeutic effect making a frequent dosing regimen necessary. As a result, frequent instillation of solution or higher drug concentration is needed to achieve the desired therapeutic response. Due to tear drainage, most of the administered dose is absorbed via the naso-lacrimal duct to the GI tract, leading to side-effects. Major advancement to overcome these disadvantages has been made by the development of in situ-forming gels. These systems consist of polymers that exhibit sol-to-gel phase transitions as a result of specific physical / chemical change induced by the physiological environment in the cul-de-sac as pH, temperature or a specific ion. Such a system can be formulated as a liquid dosage form suitable to be administered by instillation into the eye, which upon exposure to physiological conditions of eye shifts to the gel phase, thus leads to increasing the pre-corneal residence time of the delivery system and enhancing ocular bioavailability. Polaxamer is non-ionic surface active agent, and block copolymers consisting of polyethylene oxide and polypropylene oxide units. Their relatively low toxicity and capacity to form clear gels make them particularly suitable for dermatological or ophthalmic formulations as well as in the area of controlled drug delivery systems and it is known for exhibiting the phenomenon of reverse thermal gelation under a certain concentration and temperature. Though thermo sensitive copolymers are employed widely, they suffer from a major drawback of having weak mechanical strength, which leads to rapid erosion of polymer. This problem can be solved by using blends of poloxamers with

chitosan. Chitosan, a natural polysaccharide derived from naturally abundant chitin, having excellent ocular compatibility. Chitosan is a polycation on interacting with the polyanionic surface of mucosal surface of cornea it enhances the mucoadhesive properties. Gupta et al, developed timolol maleate isotonic solution base using chitosan/polaxamer that converted into gel at temperatures above 35°C and pH 6.9-7.0.

Gemifloxacin is a new fluoroquinolone that possesses enhanced activity against Gram-positive cocci, in particular Streptococcus pneumoniae. It has been shown to have higher affinity than other quinolones for S. pneumoniae topoisomerase IV, including isolates displaying resistance mutations. The aim of this study was to assess the pharmacokinetics and tissue penetration of this drug following administration of a single oral dose of 320 mg. Tissue penetration was quantified using a blister technique. Blister fluid mimics an inflammatory exudate and hence is a model of likely pharmacokinetics at the site of infection.

EXTENDED DRUG DELIVERY SYSTEM

Extended release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. Oral extended release drug delivery medication will continue to account for the largest share of drug delivery systems. Extended-release drug-delivery systems are designed to release drugs over a prolonged period employing steady-rate drug release or controlled release to achieve stable and higher therapeutic potential while minimizing adverse side effects. Extended-release NPs used in a clinical setting hold drugs either on their surface or adsorbed in a matrix that attains sustained release. Currently, hydrophobic biodegradable polymeric NPs are commonly used for the continuous supply of encapsulated.

FORMULATION AND EVALUATION OF GEMIFLOXACIN TABLETS

Procedure

Sustainer release tablets of gemifloxacin were prepared by using polymer Xanthan gum, guar gum, carbopol 937 in all formulation. The ingredients given in table, except glidant and lubricant were thoroughly mixed in mortar and pestle. The wet mass passed through sieve no.16 and c for 30-45.

Composition of prepared extended release tablets

Table 1: Composition of Gemifloxacin Sustained Release Tablets

S. No	INGREDIENTS (mg/tablet)	FORMULATIONS WITH CODES								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Gemifloxacin	320	320	320	320	320	320	320	320	320
2	Guar Gum	50	75	100	--	--	--	25	37.5	50
3	Xanthan Gum	--	--	--	50	75	100	25	37.5	50
4	Micro Crystalline Cellulose	143	118	93	143	118	93	143	118	93
5	Aerosil	6	6	6	6	6	6	6	6	6
6	Magnesium stearate	6	6	6	6	6	6	6	6	6
7	Total weight(mg)	600	600	600	600	600	600	600	600	600

"--"indicates not present

Formulation of sustained release tablets

Sustained release tablet. Were prepared by wet granulation method. The sustained tablets were prepared with prepared with guar gum, and carbopol 937 were used. The drug and polymer ratio was 1:0:5.

EVALUATION OF SUSTAINED RELEASE TABLETS

Tablets thickness

The thickness of the were weight of 10 tablets of each formulation was measured using digital veneer caliper in mm.

Weight variation

Twenty tablets were weight individually and the average weight was determined. The percentage deviation was calculate and checked for weight variation.

Hardness

Tin is determine using a Monsanto hardness tester. Pressure required to break the tablets is determine in kg/mc2

Friability

Weight amount of 20 tablets were subject to rotating drum of friability test apparatus. The drum is rotated at 25 rqm. the apparatus was operated for 4 min and reweighted the tablets. Friability was calculated using formula

F=100(Wo-W)/Wo

F=Friability

Wo=initial weight

W= final weight

In-vitro release studies

Dissolution study

The dissolution test apparatus (USB) is used. The whole assembly is kept in a jacket vessel of water maintained at 37+_ 1 C. tablets placed in to the bottom of the flask. The beaker is filled with 900 ml of 0.1N Hcl. The vessel is maintained at 100.

RESULTS AND DISCUSSION

Pre compression parameters

Pre compression parameters of all the Gemifloxacin sustained released (F1-F9) tablets were shown in excellent flow properties and it shows satisfactory results. The angle of repose ranged from 230.38′ to 390.99′, hausner ratio ranged from 1.041 to 1.305, compressibility index ranged from 8.355 to 14.973%, bulk density ranged from 0.207 to 0.701g/cc and tapped density ranged from 0.258 to 0.730g/cc. The pre-compression parameters are summarized in Table No: 2.

Table 2: Pre-Compression parameter of GFX

S. No	FORMULATIONS	Angle of repose (0)	Hausner Ratio	Compressibility Index (%)	Density (g/cc)	
					Bulk	Tapped
1	**F1**	26.56±0.78	1.041±0.23	14.973±0.05	0.701±0.33	0.73±0.88
2	**F2**	35.9±0.44	1.301±0.09	13.131±0.54	0.329±0.64	0.428±0.65
3	**F3**	39.99±0.22	1.249±0.52	9.907±0.35	0.346±0.21	0.432±0.84
4	**F4**	36.16±0.45	1.303±0.74	14.230±0.94	0.423±0.88	0.551±0.77
5	**F5**	37.19±0.54	1.305±0.08	14.389±0.55	0.321±0.41	0.419±0.54
6	**F6**	32.82±0.66	1.091±0.28	8.355±0.07	0.351±0.22	0.383±0.84
7	**F7**	34.99±0.47	1.246±0.21	12.767±0.12	0.207±0.74	0.258±0.76
8	**F8**	23.38±0.69	1.222±0.24	12.155±0.98	0.275±0.97	0.336±0.79
9	**F9**	26.56±0.27	1.263±0.48	10.833±0.35	0.266±0.54	0.336±0.13

All the values are expressed in Mean± SD, N=3

Post compression parameters

Post compression parameters of all the Gemifloxacin sustained released (F1-F9) tablets were shown within in the limits and it shows satisfactory results. The weight uniformity ranged from 597.89 to 599.98mg, thickness ranged from 3.91 to 4.06 mm, hardness ranged from 6.16 to 6.75 kg/cm2, Friability ranged from 0.14 to 0.43%, and drug content ranged from 98.99 to 101.72 mg/tablet and the results are shown in Table No: 3.

Table 3: Post Compression parameters of GFX sustained released tablets.

S. No	FORMULATIONS	Weight Uniformity (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug Content (mg/tablet)
1	**F1**	598.89±0.12	4.06±0.09	6.18±0.08	0.43±0.06	101.72±0.21
2	**F2**	597.89±0.14	4.03±0.03	6.53±0.23	0.32±0.21	100.6±0.15
3	**F3**	597.98±0.15	3.94±0.04	6.21±0.21	0.14±0.26	98.99±0.63
4	**F4**	598.45±0.18	3.98±0.03	6.75±0.06	0.20±0.68	99.24±0.75
5	**F5**	598.69±0.10	4.06±0.04	6.53±0.02	0.33±0.14	99.56±0.20
6	**F6**	599.98±0.11	4.02±0.02	6.39±0.041	0.18±0.25	99.27±0.35
7	**F7**	598.92±0.10	4.08±0.08	6.16±0.36	0.21±0.33	100.31±0.14
8	**F8**	598.90±0.18	3.91±0.07	6.42±0.03	0.32±0.45	101.22±0.54
9	**F9**	598.85±0.19	4.04±0.05	6.29±0.02	0.16±0.20	100.33±0.68

All the values are expressed in Mean± SD, N=3

In Vitro release kinetic analysis

The first order plots of the all formulations (F1-F9) were indicated linear, so they followed first orders release kinetics. The slope of the line and corresponding first order constants (K) can be calculated, which is indicative of the release rate profile. The drugs released from the formulations were evaluated by using different kinetic models. The regression coefficient (r2) obtained from First order, Higuchi and Korsmeyer-Peppas models & its corresponding constants (n) are shown in Table No: 4. To investigate the mechanism of drug released from the GFX formulations were done by plotting for square root of time on X-axis verses cumulative drug release on Y-axis as described by higuchi, for all the formulations (F1 to F9) were found to be linear, indicating the diffusion mechanism of drug released. The time on X-axis verses percent drug released on Y-axis profiles were fitted for the peppas equation. The “n” values of all the formulations (F1-F9) were between the 0.45 to 0.89, which indicates formulations follow the Non-Fickian transport system. The Gemifloxacin sustained released formulations (F1-F9) profiles were shown in Fig. 1 to 7.

Table 4: Kinetics of in vitro GFX released from sustained release tablets

S. No	FORMULATIONS	Gemifloxacin			
		First order	Higuchi	Peppas	'n' value
1	**F1**	0.925	0.975	0.757	0.950
2	**F2**	0.997	0.999	0.629	0.992
3	**F3**	0.999	0.998	0.715	0.999
4	**F4**	0.872	0.986	0.726	0.812
5	**F5**	0.851	0.965	0.986	0.733
6	**F6**	0.879	0.951	0.983	0.774
7	**F7**	0.993	0.981	0.967	0.494
8	**F8**	0.974	0.984	0.996	0.655
9	**F9**	0.998	0.985	0.998	0.707

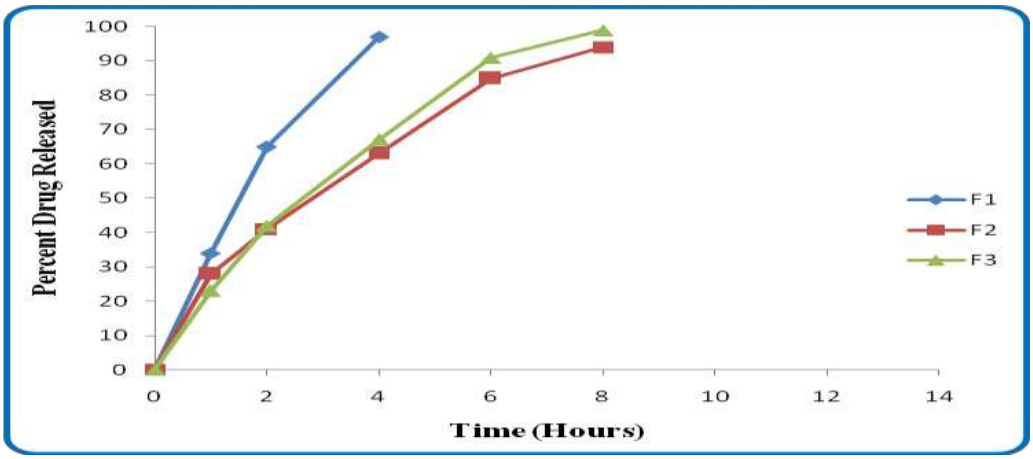

Fig 1: Gemifloxacin released profiles (Guar Gum as a Polymer) of F1 to F3.

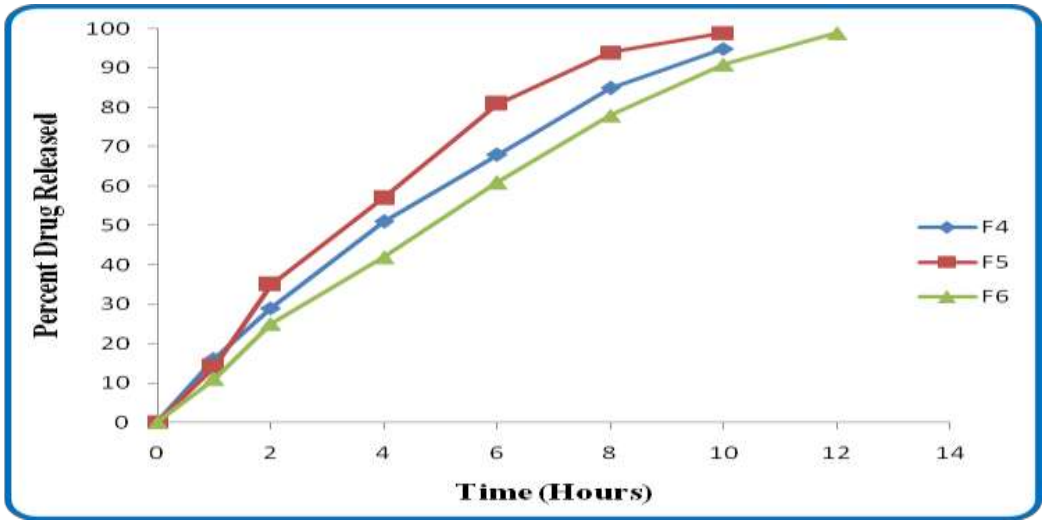

Fig 2: Gemifloxacin released profiles (Xanthan Gum as a Polymer) of F4 to F6.

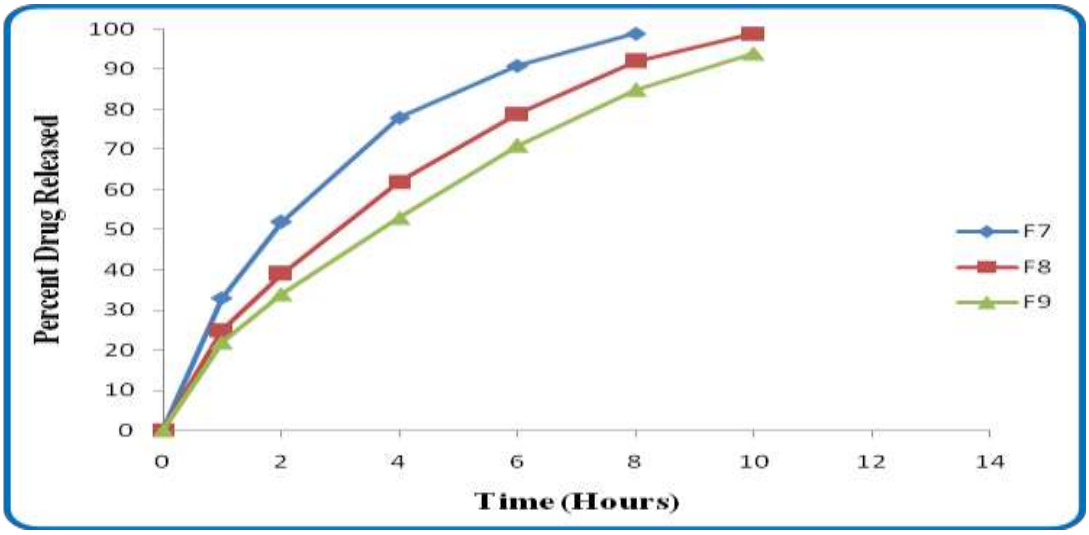

Fig 3: Gemifloxacin released profiles (Guar Gum & Xanthan Gum as Polymers) of F7 to F9.

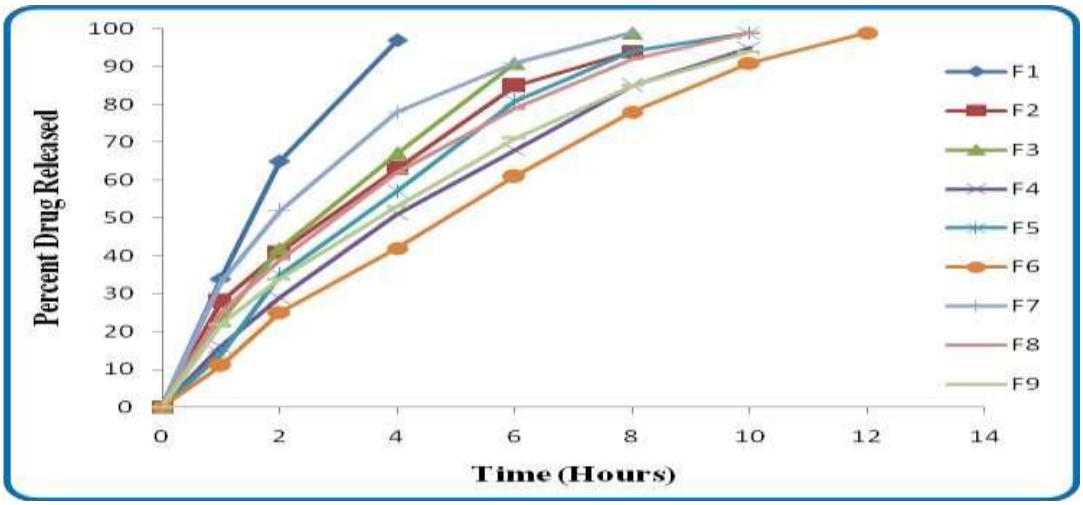

Fig 4: Comparison of the Gemifloxacin in vitro release profiles for F1 to F9.

Compatibility studies by using FT-IR

The compatibility studies should be conducted by to check the whether any compatibility problems between drugs (Gemifloxacin natural polymers (Guar gum and Xanthan gum) and excipients (MCC, Aerosil and magnesium stearate) used in present investigation. The Physical mixture of drugs, polymers and Best formulation (F6) was characterized by FTIR spectral analysis for any physical as well as chemical alteration of drug characteristics. The FI-IR spectrums (Fig. 11 and 15), it is clear that the characteristics peaks are seen in both pure drugs (GFX) and polymers (Guar gum and Xanthan gum) without any changes in their position, so there is no strong interactions between excipients, polymers and Drugs.

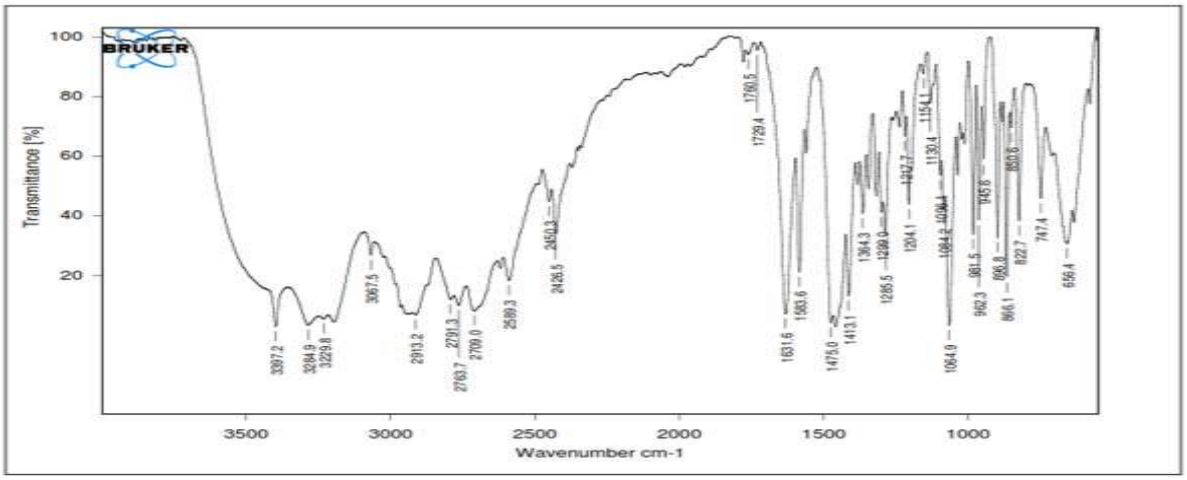

Fig 5: FTIR Spectrum for Gemifloxacin pure drug

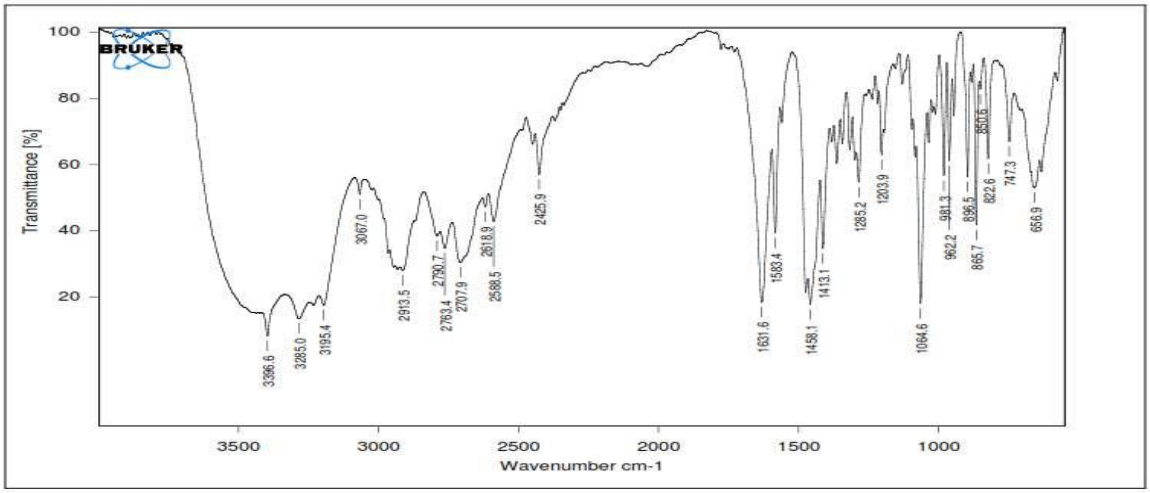

Fig 6: FTIR Spectrum for Best formulation (F6).

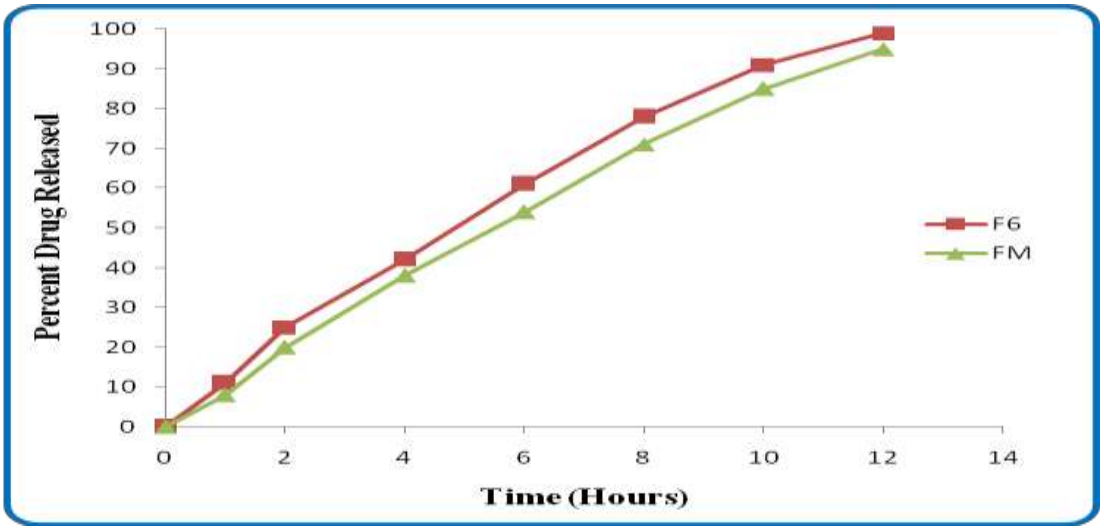

Fig 7: Comparison of the in vitro release of Optimized formulation (F6) with market formulation (FM)

SUMMARY AND CONCLUSION

The present work to aim the design, fabrication and evaluation of Gemifloxacin sustained release tablets by wet granulation technique. In this technique Guar Gum and Xanthan Gum were used as polymers for drug released upto extended time period. The Formulations F6 found to satisfy the desired criteria for GFX released from the formulation. The drugs released from the formulations and released mechanism followed for "first order kinetics & Non-Fickian diffusion mechanism" respectively. Finally to achieve a Gemifloxacin sustained released tablets and drugs released up to 12 hrs. The Comparison of the optimized formulation (F6) with market formulation (FM) is shown in Fig.7. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drug delivery system, two prerequisites would be required: Firstly single dose for the duration of treatment whether for days or weeks as with infection, diabetes or hypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.

REFERENCES

1. George M, Grass IV, Robinson JR. Sustained and controlled release drug delivery systems. New york: Marcel Dekker; 1978. p. 124-7.
2. Mishra B, Seena J, Singh S, Sankar C. Development & characterization of matrix tablets of ketorolac trometh amine. Indian Pharm. 2003;2:86-9.
3. Reddy KR, Mutalik S, Reddy S. Formulation and in vitro evaluation of sustained release nicorandil matrix tablets. AAPS PharmSciTech. 2003;4(4):480-8. 4. Merck & co. Inc., The Merck Index, an Encyclopedia of Chemicals, Drugs and Biologicals, 14th Edn., white house station, New Jersey, 2006; 756.
4. Sweetman SC. Martindale: the complete drug reference. 37th ed. London: Pharmaceutical Press; 2011. p. 306.
5. Barar FSK, ed. In: Chand S, editor and Company Ltd. Essentials of pharmacotherapeutics. 3rd ed. New Delhi; 2005. p. 550.
6. Sweetman SC. Martindale: the complete drug reference. 37th ed. London: Pharmaceutical Press; 2011. p. 1689.
7. Vergin H, Bishop-Freudling GB, Miczka M, Nitsche V, Strobel K. Arzneim Forsch Drug Res. 1985;35:1591.
8. Alighieri T, Avanessian S, Berlini S, Bianchi SG, Deluigi P, Valducci R et al. Arzneim. Forsch-Drug.
9. Al-Saidan SM, Krishnaiah YS, Satyanarayana V, Bhaskar P, Karthikeyan RS. Pharmacokinetic evaluation of guar gum based three layer matrix tablets for oral controlled delivery of highly soluble metoprolol tartrate as a model drug. Eur J Pharm Biopharm. 2004;58(3):697-703. doi: 10.1016/j.ejpb.2004.04.013, PMID 15451547.
10. Khullar P, Khar RK, Agarwalet SP. Guar gum as a hydrophilic matrix for preparation of theophylline controlled release dosage form. Indian J Pharm Sci. 1999;61(6):342-5.
11. Bumphrey G. Extremely useful" new suspending agent. Pharm J. 1986;237:665-71.
12. Chollet JL, Jozwiakowski MJ, Phares KR, Reiter MJ, Roddy PJ, Schultz HJ, Ta QV, Tomai MA. Development of a topically active imiquimod formulation. Pharm Dev Technol. 1999;4(1):35-43. doi: 10.1080/10837459908984222, PMID 10027211.
13. Wang XQ, Huang J, Dai JD, Zhang T, Lü WL, Zhang H, Zhang X, Wang JC, Zhang Q. Long-term studies on the stability and oral bioavailability of cyclosporine A nanoparticle colloid. Int J Pharm. 2006;322(1-2):146-53. doi: 10.1016/j.ijpharm.2006.05.021, PMID 16787721.
14. Junyaprasert VB, Manwiwattanakul G. Release profile comparison and stability of diltiazem resin microcapsules in sustained release suspensions. Int J Pharm. 2008;352(1-2):81-91. doi: 10.1016/j.ijpharm.2007.10.018, PMID 18061381.
15. Higuchi T. Mechanism of Sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52:1145-9. doi: 10.1002/jps.2600521210, PMID 14088963.
16. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(1):25-35. doi: 10.1016/0378-5173(83)90064-9.
17. Lee VHL. Controlled Drug Delivery Fundamentals and pplications: introduction, Marcel Dekker. New York: INC; 1987:29. (p. 2nded).
18. Banker GS, Anderson NR. The Theory and Practice of Industrial Pharmacy: Tablet, Lachman, (3rded). Bombay: Varghese Publishing House; 1990. p. 293-303.
19. John C, Morten C. The Science ofDosage Form Design, Aulton: modified release peroral dosage forms, (2nded). Churchill Livingstone; 2002. p. 290-300.
20. Vallabh Prakashan D. Brahmankar DM and Jaiswal SB.biopharmaceutics and Pharmacokinetics:pharmacokinetics. 2nd ed; 2009. p. 399-401.
21. Lee VHL. Controlled Drug Delivery Fundamentals and Applications: influence of drug properties on design. New York: Marcel Dekker, INC; 1987:16-25. (p. 2nded).
22. Ho WH, Lee HLV. Controlled Drug Delivery Fundamentals and Applications: design and fabrication of oral controlled release drug delivery system, (2nded). NY: Marcel Dekker, INC; 1987. p. 373-420.

23. Janos B, Klara P, Odon P, Geza RJ, Rok D, Stane S, Istvan E. Film coating as a method to enhance the preparation of tablets from dimenhydrinate crystals. Int J Pharm 004;269:393-401.
24. Patrick JS. Martin's Physical Pharmacy and Pharmaceutical Sciences, (3rd). Bombay: Varghese Publishing House; 1991. p. 512-9.
25. ar RK. Mohapatra S, Barik BB. Design and characterization of controlled release matrix tablets of zidovudine. Asian J Pharm Clin Res. 2009;2:54-61.
26. Higuchi T. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52:1145-9. doi: 10.1002/jps.2600521210, PMID 14088963.
27. Shah R, Magdum C, Patil SK, Chougule DD, Naikwade N. Validated Spectroscopic Method for Estimation of aceclofenac from Tablet Formulation. Res J Pharm Technol. 2008;1:430-2.
28. Omaimah MN et al. Gohary RS. Stability studies of aspirin–magaldrate double layer tablets. Pharm Acta Helv. 2000;74:351-60.