Research Article **ISSN: 2349 – 4492**

Asian Journal of Research in Biological and Pharmaceutical Sciences

Journal home page: www.ajrbps.com

https://doi.org/10.36673/AJRBPS.2021.v09.i03.A12

FORMULATION DESIGN, DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE TABLETS OF ACYCLOVIR BASED ON OSMOTICTECHNOLOGY

Sk. Moumeen*[1], M. Sunil[1], G. Sudhakara Rao[1]

[1*]Department of Pharmaceutics, Vishwa Bharathi College of Pharmaceutical Sciences, Perecherla, Guntur, Andhra Pradesh, India.

ABSTRACT

The following conclusion could be drawn from the research work carried out from the project: Osmotic tablets for acyclovir could be successfully prepared with different osmogens in different concentration and could be coated with semi-permeable polymer like cellulose acetate for the release of the drug. *In vitro* release studies were carried out for all formulations to quantify percentage cumulative release of drug. Based on the drug release profile suitable formulation was selected. The Formulation no-7 containing drug and NaCl with 1% has shown 100.1% of drug release in 24 Hrs and the drug release followed in zero order kinetics. Formulations of core tablets shown increased drug release rate with an increase in osmogen concentration. There is a good scope for the development of elementary osmotic pump system for this drug.

KEYWORDS

Acyclovir, Osmotic technology, Controlled release and Kinetics.

Author for Correspondence:

Sk. Moumeen,

Department of Pharmaceutics,

Vishwa Bharathi College of Pharmaceutical Sciences,

Perecherla, Guntur, Andhra Pradesh, India.

Email: dr.sunilmekala@gmail.com

INTRODUCTON

The Conventional oral drug delivery systems are known to provide an immediate release of drug, in which one cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug in this formulations may various significantly, depending on factors such as physico-chemical properties of the drug, they presence of excipients.

The role of drug development was taken a therapeutically effective molecule with sub- optimal physicochemical and physiological properties and develop an optimized product that will still be therapeutically effective but with additional benefits such as:

Sustained and consistent blood levels within the therapeutic window flow rate.
Enhanced bioavailability
Reduced interpatient variability
Customized delivery profiles
Decreased dosing frequency
Improved patient compliance
Reduced side effects.

Based on the mechanism action of the drug release can be classified as:

Dissolution controlled (surface eroding, surface swelling type of systems)
Osmotic drug delivery
Multi particulate systems
Enteric coated (pH dependent systems)

In this matrix system, the drug is embedded in a polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the surrounding medium.

In contrast, reservoir systems have a drug core was surrounded by a rate controlling membrane. Oral ingestion is one the oldest and most extensively used routes of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral delivery systems there is a little or no control over release of the drug. Uncontrolled rapid release of the drug may also cause local GI or systemic toxicity. Better dosage design can minimize many of the target site over a prolonged period. After absorption, allow maintenance of plasma concentration, within a therapeutic range, which minimizes side effects and reduces the frequency of drug administration. However, pH, GI motility and the presence of food in the GI tract may affect drug release from oral CR dosage forms.

CR delivery systems was provide that desired concentration of drug at the absorption site permitting maintenance of plasma concentration within the therapeutic range and reducing dosing frequency. Controlled realse products provide significant benefits over immediate release formulations including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to a simplified dosing schedule. Numerous technologies have been used to control the systemic delivery of drugs.

EVALUATION

Hardness.
Weight variation.
Uniformity of thickness.
Drug content uniformity.
In- vitro dissolution studies.
Stability studies

Evaluation of osmotic tabletHardness

The Hardness of the tablets is determined by the hardness tester. Which consists of a barrel with a compressible springs. The pointer are moving along with the gauge in the barrel at which the tablet fractures.

Weight variation

Ten tablets were selected at random and average weight were determined. They individual tablets was weighted and the individual weight was compared with an average weight.

Tablet size and Thickness

The size and thickness of the tablets was measured by using Vernier Calipers scale.

Drug content analysis

Five tablets weighted and crushed in a mortar then weighed powder contained equivalent to 200mg of drug transferred in 100ml of phosphate buffer to give a concentration of 100µg/ml. Absorbance measured at 254nm using UV- visible spectrophotometer.

***In vitro* dissolution studies**

The dissolution fluid was 800ml 0.1N HCL for first 2hrs then replaced with phosphate buffer pH 6.8 at a speed of 60rpm and a temperature of 38ºC was used in each test. The dissolution experiments was conducted in triplicate. For all tests 5ml samples of the test medium were collected at set intervals (1, 2, 4, 6, 8, 10, 12hrs) and was replaced with equal volume of phosphate buffer pH 6.8. The samples were analyzed at 254nm using a UV spectrophotometer.

***In vitro* drug release studies**

Apparatus used: USP II dissolution test apparatus
Dissolution medium volume: 800ml
Volume temperature: 37º±0.5ºC
Speed of basket paddle: 60rpm
Sampling intervals: (1, 2, 3, 4, 6, 8, 10 and 12 hrs)
Sample withdrawn: 5ml
Absorbance measured: 254nm

Kinetic Analysis of Dissolution Data

Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$C = K_0 t$ (3)

Where, K_0 is zero-order rate constant was expressed in units of concentration/time and t is the time.

$Q = KHt^{1/2}$ (4)

The following plots was made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model);

Log cumulative of % drug remaining vs. time (First order kinetic model); Cumulative % drug release vs. square root of time (Higuchi model);

Mechanism of drug release

A simple relationship in which described drug release from a polymeric system Eq. (5). To find out that the mechanism of drug release, first 70% drug release data was fitted in Korsmeyer–Peppas model.

$M_t / M_\infty = Kt^n$ (5)

where M_t / M_∞ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent.

RESULTS AND DISCUSSION

Evaluation of tablets hardness

The prepared tablets in all this formulations was possessed by good mechanical strength with sufficient hardness in the range of 6.9 to 7.5kg/sq cm.

Friability

Friability values below 1% were an indication of good mechanical resistance of the tablets.

Weight Variation

The tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weight variation in all the eight formulations was found to be 398 to 402mg, which was in pharmacopoeial limits of ±5% of the average weight.

Drug Content

The percentage drug content of all the tablets was found to be around 99 % of acyclovir which was within the acceptable limits.

It is evident that after coating with semi permeable membrane of Cellulose acetate, the increase in concentration of osmogen NaCl leads to increase in drug release from the tablet due to the osmotic effect. Above the all formulations F7 were optimized based on maximum drug release.

Table No.1: Diffusion exponent and solute release mechanism for cylindrical shape

S.No	Diffusion exponent (n)	Overall solute diffusion mechanism
1	0.45	Fickian diffusion
2	0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
3	0.89	Case-II transport
4	n > 0.89	Super case-II transport

Table No.2: Dissolution data for core tablet

S.No	Time in min	F1	F2	F3	F4	F5	F6	F7	F8
1	0	0	0	0	0	0	0	0	0
2	5	2.5	1.8	6.3	5.8	9.4	1.2	1.6	1.4
3	10	10	6.9	11.4	10.9	16.8	6.8	5.2	6.4
4	15	16	12	19.8	18.3	22	12.3	11.8	12.4
5	30	20	19	26.3	24.8	29.8	19.9	16.3	14.9
6	45	28	24	32.8	32.4	36.9	24.8	22	19
7	60	35	30	40	38	42	36	24	20

Table No.3: Dissolution studies for osmotic tablets

S.No	Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8
1	1	10.6	11.6	7.2	30.6	29.7	6.3	5.7	5.0
2	2	39.8	40.7	17.1	49.9	48.2	15.4	11.9	10.6
3	4	70.3	68.2	29.2	60.2	59.3	26.1	20.2	21.4
4	6	100.1	99.1	50.8	90.1	70.8	40.6	30.5	29.7
5	8	-	-	73.7	100.1	89.6	61.1	48.9	50.2
6	10	-	-	88.22	-	100.3	73.1	52.2	64.8
7	12	-	-	99.26	-	-	89.92	62.1	76.1
8	16	-	-	-	-	-	99.5	70.8	81.2
9	20	-	-	-	-	-	-	88.1	89.9
10	24	-	-	-	-	-	-	100.1	95.9

KINETIC STUDIES FOR OPTIMIZED FORMULATION (F7)

Table No.4: Release kinetics for the optimized formulation F7

S.No		Zero	First	Higuchi	Peppas
		% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C VsLog T
1	Slope	4.19896522	- 0.066232764	21.8593371	1.156798697
2	Intercept	5.273325668	2.1811698	- 14.40868403	0.520660117
3	Correlation	0.988774605	- 0.900228846	0.978681504	0.941000913
4	R2	0.97767522	0.810411974	0.957817487	0.885482718

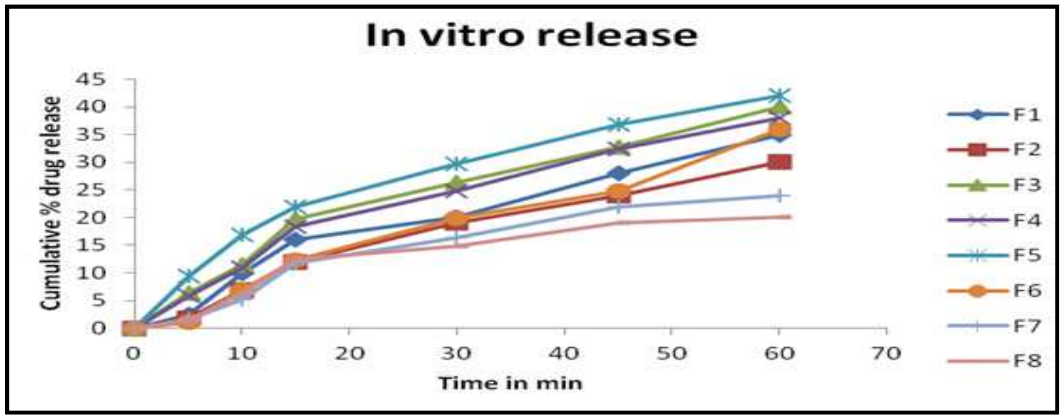

Figure No.1: Dissolution graph for core tablets

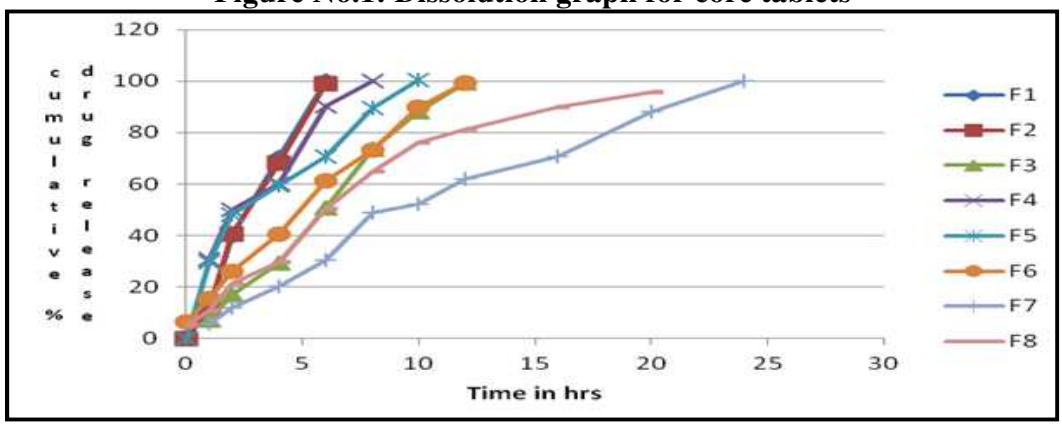

Figure No.2: Dissolution graph for osmotic tablets

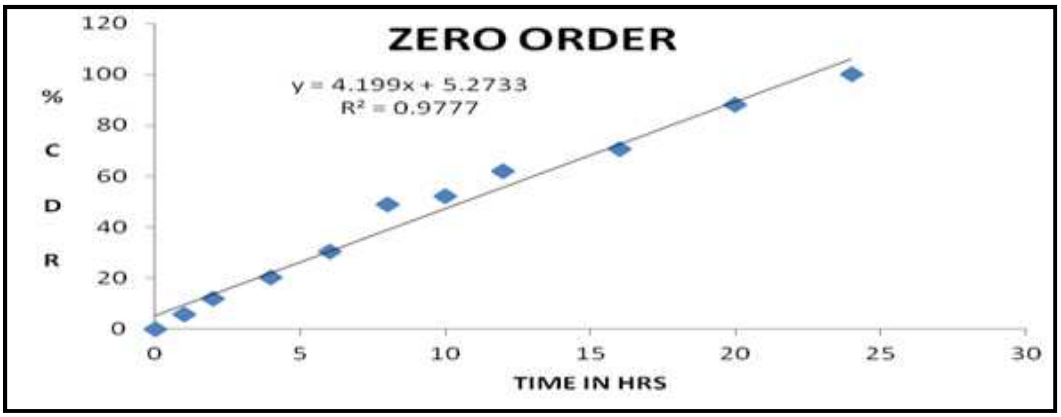

Figure No.3: Zero order plot for optimized formulation

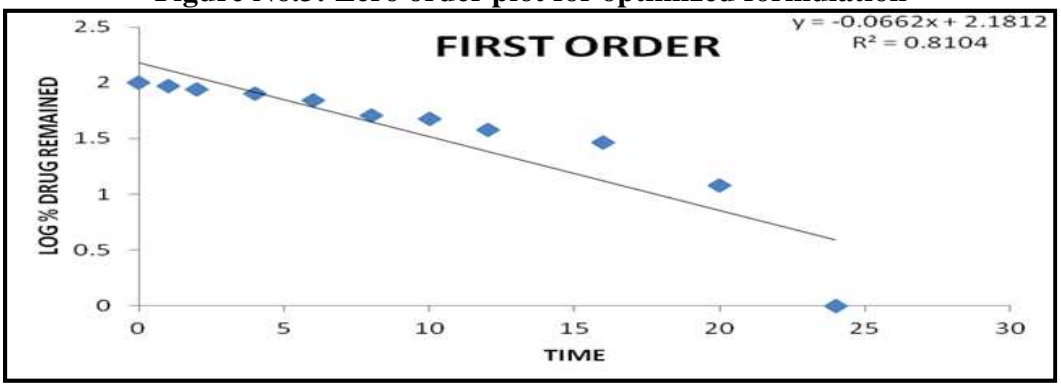

Figure No.4: First order plot for optimized formulation

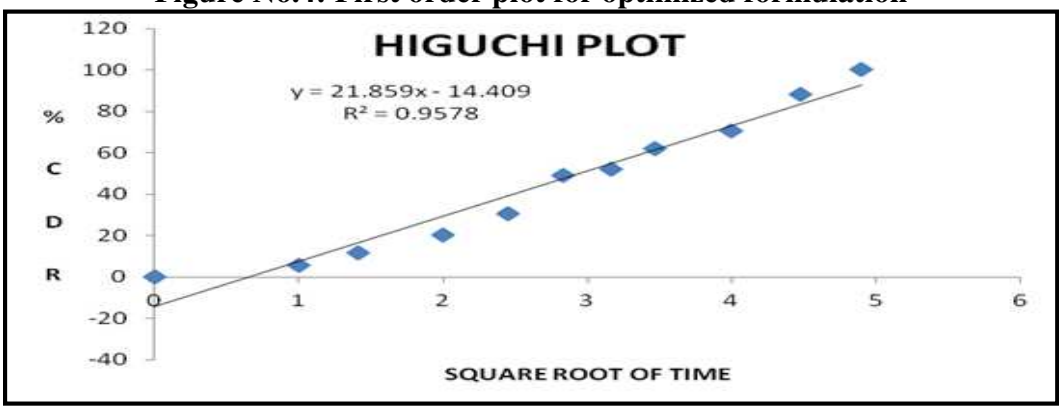

Figure No.5: Higuchi plot for optimized formulation

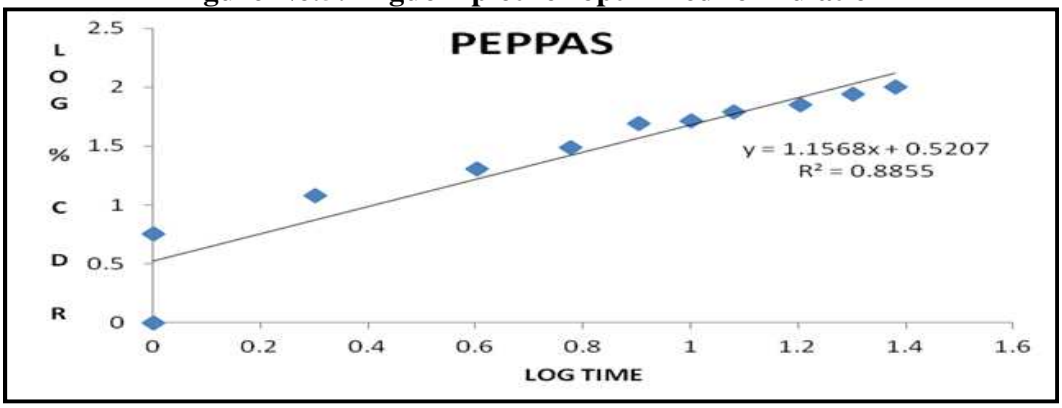

Figure No.6: Peppasplot for optimized formulation

CONCLUSION

The following conclusion could be drawn from the research work carried out from theproject:

Osmotic tablets for acyclovir could be successfully prepared with different osmogens in different concentration and could be coated with semi-permeable polymer like cellulose acetate for the release of the drug.

In vitro release studies were carried out for all formulations to quantify percentage cumulative release of drug. Based on the drug release profile suitable formulation was selected. The Formulation no-7containing drug and NaCl with 1% has shown 100.1% of drug release in 24 Hrs and the drug release followed in zero order kinetics.

Formulations of core tablets shown increased drug release rate with an increase in osmogen concentration.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Department of Pharmaceutics, Vishwa Bharathi College of Pharmaceutical Sciences, Perecherla, Guntur, Andhra Pradesh, India for providing necessary facilities to carry out this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Ayer A D, Balkie H K. Method and apparatus for forming a hole in a drug dispensing device, *US patent 5,071,607,* 1991.
2. Bindschaedler C, Gurny R, Doelker E. Mechanically strong films produced from cellulose acetate latexes, *Journal of Pharmacy and Pharmacology,* 39(5), 1987, 335-338.
3. Cardinal J R, Herbig S M, Korsmeyer R W, Lo J, Smith K L, Thombre A G. Use of asymmetric membrane in delivery devices, *US patent 5, 612,059,* 1997.
4. Cardinal J R, Herbig S M, Korsmeyer R W, Lo J, Smith K, Thombre A G. Asymmetric membrane in delivery devices, *US patent 5, 698,* 220, 1997.
5. Chen R, Theeuwes F. Osmotic device with laser drilling, *US patent 5, 736, 159,* 1982.
6. Dong L, Sha K, Wan J W. Novel osmotic delivery systems: L-OROS softcap, *Proceedings of the 27th International Symposium on Controlled Release of Bioactive Materials, Controlled Release Society,* 2000.
7. Prabhakaran D, Paramjitsingh, Parijat Kanaujia, Jaganathan K S, Amit Ravat, Suresh P. Vyas. Modified push-pull osmotic system for simultaneous delivery of theophylline and salbutamol: Development and *in-vitro* characterization, *International Journal of Pharmaceutics,* 284(1-2), 2004, 95-108.
8. Prabhakaran D, Paramjitsingh, Parijat Kanaujia, Suresh P. Vyas. Effect of hydrophilic polymers on the release of diltiazem HCl from elementary osmotic pumps, *International Journal of Pharmaceutics,* 259(1-2), 2003, 173-179.
9. Garg A, Gupta M, Bhargava H N. Effect of formulation parameters on the release characteristics of Propranolol from asymmetric membrane coated tablets, *European Journal of Pharmaceutics and Bio Pharmaceutics,* 67(3), 2007, 725-731.
10. Guo J. Effects of plasticizers on water permeation and mechanical properties of cellulose acetate: Antiplasticization in slightly plasticized polymer film, *Drug Dev. Ind. Pharm,* 19(13), 1993, 1541-1555.
11. Gupta L, Atkinson F, Theeuwes P, Wong, Longstreth J. A review on significant in vitro and *in vivo* correlation for a verapamil oral osmotic system, *Eur. J. Pharm. Biopharm,* 42(1), 1996, 74-81.
12. Hajare A, Vani H, Benson G, Mukesh. Design and evaluation of sustained release tablets of Diltiazem hydrochloride, *J. Pharma, Sci,* 2004, 583-596.
13. Hanlon J C, Benson, Galiria K, Schein. Formulation and evaluation of osmatic controlled delivary systems HCl extended release, *J. Pharm. Sci,* 517, 2008, 534-542.
14. Haslam J L, Rork G S. Controlled porosity osmotic pump, *US patent 4, 880, 631,* 1989.
15. Herbig S M, Cardinal J R, Korsmeyer R W, Smith K L. Asymmetric- membrane tablet

coating for osmotic drug delivery, *J. Controlled Release,* 35(2-3), 1995, 127-136.
16. http://www.drugbank.com, URL: www.druglist.ca/drugs/Propranolol tablets.html.
17. Hindustan Abdul Ahad, Sreeramulu J. Design and evaluation of sustained release matrix tablets of Glimepiride based on combination of natural and synthetic polymers, *IJABPT,* 1(3), 2010, 770-777.
18. Kanagale P, Braj L B, Mishra A, Davadra P, Kini R. Formulation and optimization of porous osmotic pump–based controlled release system of Oxybutynin, *American Association of Pharmaceutical Scientists Pharma Sci Tech,* 8(3), 2007, E1-E7.
19. Khan A B, Nanjundaswamy N G. Formulation and evaluation of sustained release matrix tablets of propranolol hydrochloride using sodium carboxymethyl guar as r rate sustaining polymer, *Arch Pharm Sci and Res,* 1(2), 2009, 203-206.
20. Kumar Guarve, Gupta G D. Development of *In-vitro* Evaluation of osmotically controlled oral drug delivery system of carvedilol, *International Journal of Pharmaceutical Science and Drug Research,* 1(2), 2009, 80-82.
21. Leon L, Herbert A, Liberman, Joseph L, Kanig. The theory and practice of industrial pharmacy, 3rd Edition, 1986, 293-302.
22. Lindstedt B, Ragnarsson G, Hjartstam J. Osmotic pumping as a release mechanism for membrane-coated drug formulations, *Int. J. Pharm,* 56(3), 1989, 261-268.
23. Liu L, Khang G, Lee B, Rhee J M, Lee H B. Nifedipine controlled delivery by sandwiched osmotic tablets system, *J. Control Release,* 68(2), 2000, 145-156.
24. Liu L, Khang G, Rhee J M, Lee H B. Monolithic osmotic tablet system for nifedipine delivery, *J. Control. Release,* 67(2-3), 2000, 309-322.
25. Liu L, Wang X. Solubility modulated monolithic osmotic pump tablet for atenolol delivery, *Eu. J. Ph Bio,* 68(2), 2008, 298-302.
26. Mishra B, Bharati V, Bakde P N, Singh, Kumar P. Release of Tramodol hydrochloride from matrix tablets containing xanthan gum and micro crystalline cellulose, *Pharm Dev and Tech,* 4(3), 1999, 313-324.
27. Madhusmruti K, Santanu C, Anuradha S, Debashisha P, Nazia K, Santosh K. Development of propranolol hydrochloride matrix tablets: aninvestigation on effects of combination of hydrophilic andhydrophobic matrix formers using multiple comparison analysis, *Int J. of Pharma Sci Review and Research,* 1(2), 2010, 1-6.
28. Mahalaxmi R, Phanidhar Sastri, Ravikumar, Atin Kalra, Pritam Kanagale D, Narkhede R. Enhancement of dissolution of glipizide from controlled porosity osmotic pump using a wicking agent and a solubilizing agent, *International Journal of Pharma Tech Research,* 1(3), 2009, 705-711.
29. Martin A. Factors affecting release on osmotic systems, 1993.
30. Mina Rani and Brahmeshwar Mishra. Comparative *in-vitro* and *in-vivo* evaluation of matrix, osmotic matrix, and osmotic pump tablets for controlled drug delivery of diclofenac sodium, *AAPS Pharma Sci Tech,* 5(4), 2004, 153-159.
31. Mina Rani and Rahul Surana. Development and biopharmaceutical evaluation of osmotic pump tablets for controlled delivery of diclofenac sodium, *Acta Pharm,* 53(4), 2003, 263-273.
32. Ramakrishna N, Mishra B. Plasticizer effect and comparative evaluation of cellulose acetate and ethylcellulose-HPMC combination coatings as semi-permeable membranes for oral osmotic pumps of naproxen sodium, *Drug Development and Industrial Pharmacy,* 28(4), 2002, 403-412.
33. Nurten Ozdemir, Jfilide Sahin. Design of a controlled release osmotic system for ibuprofen, *International Journal of Pharmaceutics,* 158(1), 1997, 91-97.
34. Ouyang D, Nie S, Li W, Guo H, Liu H, Pan V. Design and evaluation of compound metformin/glipizide elementary osmotic tablets, *J Pha Pharm,* 57(7), 2005, 817-820.
35. Owen S, Rowe R, Sheskey P. Pharmaceutical Excipients, 245, 267, 389.

36. Ozturk A G, Ozturk S S, Palsson B O, Wheatley T A, Dressman J B. Mechanism of release from pellets Coated With an ethyl cellulose- based film, *J. Controlled. Release,* 14(3), 1990, 203-213.
37. Parikh M. Handbook of Pharmaceutical excipients, 81, 121-124.
38. Rao P B, Geetha M, Purushothama N, Utpal. Optimization and development of swellable controlled porosity osmotic pump tablet for Theophylline, *Trop Jour of Pharma Res,* 8(3), 2009, 247-255.
39. Rose S, Nelson J F. A continuous long-term injector, *Au. J. Ex. Bio,* 33(4), 1955, 415-419.
40. Rajan K Verma, Sanjay Garg. Development and evaluation of osmotically controlled oral drug delivery system of Glipizide, *Euro Jour of Pharma and Biopha,* 57(3), 2004, 513-525.
41. Santus G, Baker R W. Osmotic drug delivery principle of osmosis a review of the patent literature, *J. Control. Rele,* 35(1), 1995, 1-21.
42. Sastry S V, DeGennaro M D, Reddy I K, Khan M A. Drug Dev. Ind. Higuchi pumps, 23, 1997, 157-165.
43. Srinath P, Karar V. Osmogens CR preparations, *Int J. of Pharm,* 175(1), 1998, 95-107.
44. Suvakantha Dash. Kinetic modeling on drug release from controlled drug delivery systems, *Acta Poloniae Pharmaceutical Drug Research,* 67(3), 2010, 217- 223.
45. Theeuwes F. Elementary osmotic pump, *J. Pharm Sci,* 64(12), 1975, 1987-1991.
46. Theeuwes F, Ayer A D. Osmotic system having laminar arrangement for programming delivery of active agent, *US patent 4, 008, 719,* 1977.
47. Theeuwes F, Swanson D R, Guittard G, Ayer A, Khanna S. Osmotic delivery systems for the beta-adrenoceptor antagonists metoprolol and oxprenolol: Design and evaluation of systems for once-daily administration, *Br. J. Clin. Pharrmacol,* 19(2), 1985, 69S-76S.
48. Verma R K, Garg S. Current status of drug delivery technologies and future directions, pharm, Technol.-On Line (http://www.pharmaportal.com), 2001, 1-14.
49. Verma R K, Zentner. Studies on formulations and evaluation of Controlled porosity osmotic pumps of nimesulide, *Pharmazie,* 54(1), 1999, 74-75.
50. Wrong, Cortese, Theeuwes F. Osmotic device for administering push pull osmatic pump, 4, 1986, 765, 989.
51. Yaw B H, Yi-Hung T, Wan C Y, Jui-Sheng C, Pao-Chu W, Kozo T. Once- daily propranolol extended-release tablet dosage form: Formulation design and *in vitro/in vivo* investigation, *Eur J of Pharmaceutics and Biopharmaceutics,* 58(3), 2004, 607-614.
52. Yong Gan, Weisan Pan, Mingchun Wei, Ruhua Zhang. Cyclodextrin complex osmotic tablet for glipizide delivery, *Drug Development and Industrial Pharmacy,* 28(8), 2003, 342-348.
53. Yan Zhang, Zhirong Zhang, Fang Wu. A novel pulsed-release system based on swelling and osmotic pumping mechanism, *Journal of Controlled Release,* 89(1), 2003, 47-55.
54. Zentner G S, Rork, Himmelstein K J. Controlled Release porosity osmotic pump, *J. Control. Release,* 1(4), 1985, 269-282.
55. Zentner G M, Rork G S, Himmelstein K J. Controlled porosity osmotic pump, *US patent 4, 968, 507,* 1990.
56. Zentner G M, Rork G S, Himmelstein K J. Osmotic flow through controlled porosity films: An approach to delivery of water soluble compounds, *J Control. Release,* 2, 1985, 217-229.

Please cite this article in press as: Sk. Moumeen *et al*. Formulation design, development and evaluation of controlled release tablets of acyclovir based on osmotic technology, *Asian Journal of Research in Biological and Pharmaceutical Sciences,* 9(3), 2021, 81-88.