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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF TRIPLE LAYERED MATRIX TABLET OF ACECLOFENAC USING GUM ACCACIA AS CORE MATERIAL

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ABSTRACT

The aim of present work was to develop once daily sustained release matrix tablet of aceclofenac by wet granulation technique using gum acacia. Aceclofenac sodium being the newer derivative of diclofenac having short biological half life (4hrs.), so it require more than one dose per day to maintain therapeutic dose. Total four formulations of aceclofenac matrix tablet were prepared using different concentration of gum acacia and evaluated for various parameters like weight variation, hardness, swelling index, friability, percent drug release and various release profile like zero order, first order, higuchi's, and koshemeyrs-peppas studied. All the evaluation parameters met pharmacopeial specifications and through dissolution studies it was concluded that MTX1showed height percent drug release and MTX4 showed lowest percent drug release at the end of 8 hrs. Matrix tablet of aceclofenac was successfully prepared and evaluated and it can be concluded that matrix tablet prepared with gum acacia showed release rate for a prolonged time and can be of great importance for "once daily" tablet to reduce side effects and toxicity related with NSAIDs.

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INTRODUCTION

The main objective of this work was to formulate & evaluate multi-layered matrix tablet of aceclofenac to achieve sustained release of drug for a longer period of time, so as to maintain the plasma drug concentration constant for the whole day. It also helps in decreasing the dosing frequency there by increasing patience compliance. Aceclofenac have a very short half life of only 4 hours so it can not maintain the plasma drug concentration at the therapeutic levels for a longer period of time. Now a days gums are widely used natural excipients for conventional and noval dosage forms due to their chemically inert, nontoxic, less expensive and biodegradable nature. (Lachman *et al*., 1990), (Kamboj *et al*, 2009) Gum Arabic is also known as acacia gum, made of hardened sap of various species of the acacia tree. Gum Arabic is a complex mixture of glycoprotein polysaccharides collected from two related species namely Acacia Senegal and Acacia seyal (Goswami *et al.,* 2014; Higuchi *et al.,* 1961). The present study aims to develop triple-layer sustained release matrix tablets using hydrophilic natural polymer gum acacia for core matrix and HPMC K-15M, NaCMC and Ethyl cellulose (EC) and PVP-K30 for preparing bottom and top layers.

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MATERIALS AND METHODS

Aceclofenac sodium, Acacia gum and HPMC K-15 were obtained as gift samples from Windlass Pharmaceuticals, Dehradun, Macloides Pharmaceuticals, Baddi (Himanchal Pradesh), Garhwal Traders', Dehradun respectively. EC, Poly vinyl pyrrolidone K –30 (PVP), NaCMC, were of analytical grade.

Preparation of Matrix Tablets (Semalty M, Bisht T *et al.,* 2012)

Triple layer matrix tablets were prepared in a three step process as followed

Triple layer matrix tablet is prepared in three steps. First core granules were prepared using aceclofenac sodium with gum acacia. Then the upper layer granules and bottom layer granules were prepared using HPMC K-15 and NaCMC as release retardant layer. 20 mg aceclofenac drug was used in each upper and bottom layer granules and 60 mg drug was used in core layer so that drug from the core granules will be released slowly and produce a sustained effect for 12 hrs.

Preparation of aceclofenac sodium matrix core granules

Core granules were prepared by wet granulation process using Acacia gum in different ratio with aceclofenac sodium. For

formulation lactose was used in different concentration as diluents, PVP-K-30 (3%) was used as binding agent. Magnesium Stearate (5 mg) was incorporated as lubricant and talc (5 mg) was used to improve flow property.

Preparation of bottom and upper layers granules

The release layer containing HPMC k-15, Na CMC was prepared by wet granulation method. The polymers and 3% PVP-K30 paste were mixed and passed through sieve no. 14 and dried at 50^{o}C for 1 hour.

Preparation of triple-layered matrix tablet

65 mg of bottom: 100 mg core: 65 upper were compressed in single punch machine, respectively. Initially the volume of the die was adjusted equivalent to total weight of three layer matrix tablet. Then pre-weighed amount of granules equivalent to bottom layer were compressed and upper punch is lifted slightly and core material is placed and compressed and finally upper layer granules were compressed.

Evaluation of prepared granules: (Lachman *et al.*, 1990)

- Angle of repose
- Tapped density
- Bulk density
- Carr's index
- Hauser's ratio

Angle of repose

Determined was Angle of repose by using fixed funnel method. The fixed funnel method employ a that was secured funnel with its at a given tip height (2cm), above the that was placed on a flat horizontal graph paper surface. A tablet blend Granules were carefully poured through the funnel until the apex of the conical pile just the tip touches of the funnel. With r the radius being of the base of the conical pile. Angle of repose was calculated the following equation using.

$$\tan \theta = h/r$$

h = Height of pile, **r** = Radius of pile & **θ**=Angle of repose

Bulk density

The bulk was determined by density a weighed quantity pouring of tablet blend into graduated cylinder & measuring the height. On the bulk density is the ratio of mass of tablet blend to bulk volume.

$$Db = M/Vb$$

Where, **M** and **Vb** are mass of powder and bulk volume of the powder respectively

Tapped Density

The Tapped is ratio density of mass blend of tablet to volume of tapped tablet blend. Amount tablet Accurately weighed of poured blend in graduated cylinder & height is measured. Allowed to 100tap then was cylinder its own under weight a hard onto surface. The was continued tapping until no further change in height was noted.

$$Dt = M / Vt$$

Where, **M** and **Vt** are mass of powder and tapped volume of the powder respectively.

Hausner's Ratio

Hausner's ratio the flow measured properties of powder & indicates by ratio the of tapped to bulk density density. The Hausner's ratio was determined by the given formula

Carr's Index (Compressibility Index)]

The compressibility is the of powder to ability decrease in volume under pressure density using bulk & density the tapped compressibility of powder were determined percentage, is compressibility which given as Carr's index. That is related to indirectly the flow relative rate. Carr's determined compressibility formula index was by the given.

Evaluation of Aceclofenac Matrix Tablets (Lachman *et al*, 1990; Aulton, 2007)

Swelling index

Swelling studies were carried out for assessing the extent of swelling for the different formulations. A matrix, upon contact with an aqueous solution, undergoes wetting which starts from the surface followed by the progression into the inner core of matrix through microscopic pores. The nature of the polymer plays an important role in this swelling process of the matrix tablets. The presence of water in the polymer causes a certain amount of stress, resulting in hydration of the polymer, which starts to swell yielding a gelatinous viscous layer. The percent swelling was determined by the following equation.

$$S\% = Ws - Wd \times 100$$

Where, Ws= weight of tablet after swelling
Wd= weight of tablet before swelling

Weight variation

Weight variation test was performed for twenty tablets from each batch and average values were calculated and then sum of individual weight was calculated. Then the difference is calculated to determine.

$$(W_{20} - W_{avg})/W_{20} * 100$$

Where W_{20} = Total weight of 20 tablet
W_{avg} = Avg weight of 20 tablet

Friability test

Friability test was performed using Roche friabilator. Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute. After 100 revolutions the tablets were dusted and reweighed. The percentage friability was determined using formula:

$$\% \text{ Friability} = W_0 - W_t / W_0 \times 100$$

Where Wo and Wt are initial and final weight respectively, before and after hundred revolutions

Drug content

Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of aceclofenac was taken in a 100 ml volumetric flask and made up to the volume with pH 6.8 phosphate buffer.

The screw knob was moved forward until the tablet broke and the force required for breaking the tablet was noted.

Disintegration test

Disintegration time is the time taken by a tablet to break up into smaller particles.

Various formulations and evaluations tables

Table 1. Composition of matrix tablets using gum acacia and excipients

Ingredients (mg)	MTX1	MTX2	MTX3	MTX4
Drug	100	100	100	100
Gum acacia	6	12	18	24
HPMC K-15	50	50	50	50
NaCMC	50	50	50	50
Lactose	24	18	12	6
Talc	qs	qs	qs	qs

MTX = matrix tablet of of gum acacia, NaCMC = sodium carboxy methyl cellulose, HPMC K-15= hydroxyl propyl methyl cellulose K-15, PVP-K30 = polyvinyl pyrrolidone-K30

Table 2. Evaluations of prepared granules

Code	Bulk Density (gm/ml)	Tapped Density(gm/ml)	Carr's Index. (%)	Hausner's ratio	Angle of Repose (θ) AF1
MTX1	0.68± 0.545	0.81± 0.545	16.04± 0.545	1.19± 0.545	27.34± 0.545
MTX2	0.17± 0.545	0.86± 0.325	17.44± 0.545	1.21± 0.545	25.80± 0.545
MTX3	0.73± 0.545	0.90± 0.435	18.89± 0.545	1.23± 0.545	26.59± 0.545
MTX4	0.72± 0.545	0.93± 0.145	22.25± 0.545	1.29± 0.545	24.88± 0.545

SD = ±5 (n)

Table 3. Result of various evaluation parameters

Formulations	Avg. wt of tablet(mg)	Friability(%)	Hardness kg/cm^2)	Drug content (%)	Swelling index (%)	Thickness (mm)
MTX-1	229 ± 0.545	0.754±.015	5.8±.005	85.5±2.31%	21±.103	5.9±.003
MTX-2	230 ± 0.346	0.984±.032	4.2±.000	78.92±1.62%	29.4±.101	4.2±.001
MTX-3	227 ±0.134	0.551± 025	5.9± 001	81.23±2.54%	36.1± 009	5.2± 003
MTX-4	232 ±0.193	0.681± 012	4.1± 003	65.78±3.45%	42± 023	5.1± 002

SD = ±5 (n)

Table 4. Calculation of percent drug release of all the four formulations

Time	MTX 1	MTX 2	MTX 3	MTX 4
30	9.13	8.45	6.58	5.9
60	17.95	16.08	14.21	11.83
120	33.08	27.82	24.08	22.72
180	47.39	41.16	37.54	35.16
240	58.32	52.21	47.62	44.22
300	72.49	68.92	61.11	59.42
360	87.65	78.14	72.53	68.12
420	94.36	84.86	82.14	79.08
480	97.78	95.4	87.25	85.72

The contents were agitated in a magnetic stirrer at 37°C for 24 hours. At the end of 24 hours content were analyzed spectrophotometrically at 274 nm after suitable dilutions (Table 2).

Thickness test

Tablet thickness should be controlled within a ±5% variation of a standard value. Vernier callipers were used to determine the thickness of tablet.

Hardness test

The tablet's hardness was measured by Monsanto hardness tester. For measuring the hardness tablet to be tested was held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero.

The USP disintegration apparatus was used to determine the disintegration time. Matrix tablet of aceclofenac shows the disintegration time between 2-3 hours (2.56 ± 0.35, n = 2).

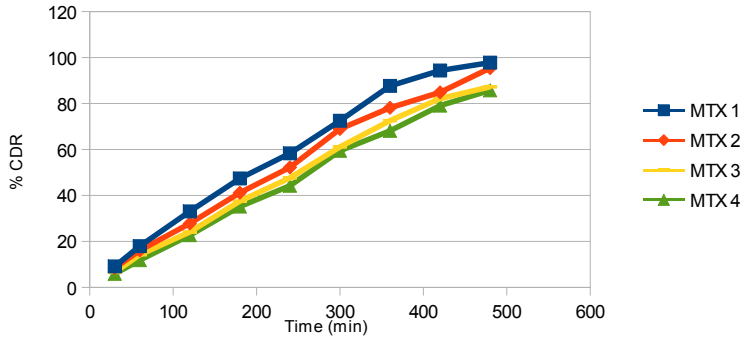
In-Vitro Drug Release Studies

In-vitro dissolution studies prepared tablets were performed in triplicate in a USP XXIII six station dissolution test apparatus (Veego Model No.6 DR, India) at 100 rpm and at 37°C ± 1°C using 900 ml of pH 6.8 phosphate buffer as dissolution medium for 8 h. Aliquots of 5 ml were withdrawn at predetermined time intervals and replaced with an equivalent amount of fresh dissolution media maintained at the same temperature. The samples were filtered, diluted suitably and then analyzed by measuring the absorbance at 274 nm by UV spectrometer (Shimadzu UV-1800).

Table 5. Calculation of cumulative drug release, percent cumulative drug release, log of cumulative drug release, square root of time and log of time

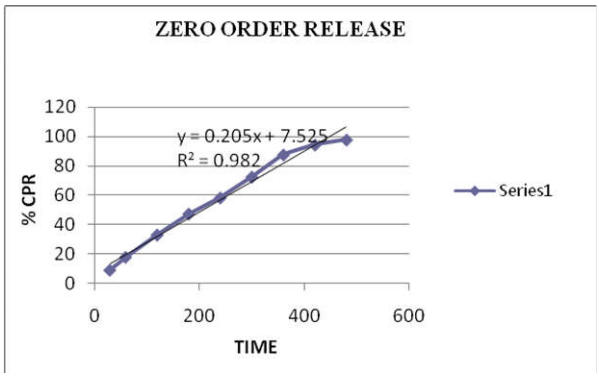
TIME	CPR	CPRU	Log CPRU	SQRT	Log T
30	9.135849057	90.864150943	1.9583926	5.4772256	1.4771213
60	17.95308688	82.04691312	1.9140622	7.7459667	1.7781513
120	33.08489908	66.915100921	1.8255241	10.954451	2.0791812
180	47.39091049	52.609089513	1.7210608	13.416408	2.2552725
240	58.3233699	41.676630101	1.6198926	15.491933	2.3802112
300	72.4956165	27.504383502	1.4394019	17.320508	2.4771213
360	87.65301009	12.346989908	1.0915611	18.973666	2.5563025
420	94.36988153	5.630118473	0.7505175	20.493902	2.6232493
480	97.7835498	2.2164501975	0.345658	21.908902	2.6812412

Various graphical representations of comparative studies

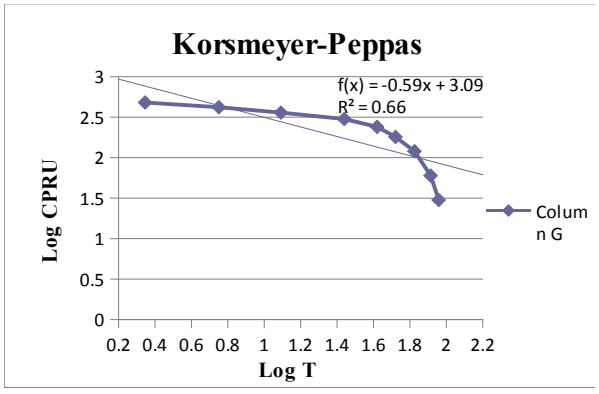


Graph 1. Percent drug release Vs time graph

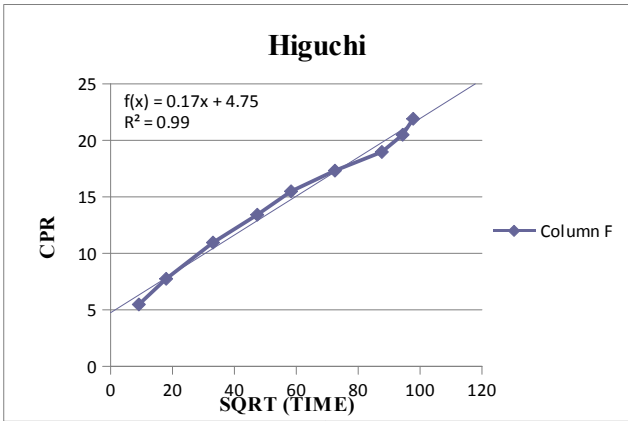
Kinetics study of MTX1 formulation



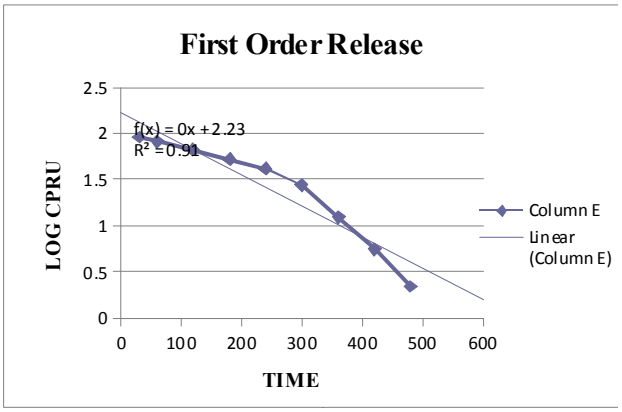
Graph 2. Percent cumulative drug release Vs time (zero order release)



Graph 3. Percent log of cumulative drug release Vs log of time (Korsmeyer-Peppas model)



Graph 4. Percent cumulative drug release Vs square of time (Higuchi model)



Graph 5. Percent log of cumulative drug release Vs time (first order release)

RESULTS AND DISCUSSION

Four different formulations using different concentration of gum acacia were formulated and evaluated. From table 1 and table 2 various conclusions were observed. Flow property of granules was found very well. Average weight of tablet was 230 mg with slight variations. Highest percent friability was found in MTX2 (0.984±.032). Highest amount of drug content was found in MTX1 (85.5±2.31). Thickness of the tablet was within the range. Highest percent drug release of found in MTX1 (97.78) and lowest percent drug release was in case of MTX4 (85.72). The swelling index was found to be increased with the time. The weight gain by tablet was increased proportionally with rate of hydration up to 3 hours. Later on, it was found to be decreasing gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. It was also observed that the swelling index was directly proportional to the gum concentration. The release of drug from Acacia gum based matrix tablet decreases as the gum concentration increases. The delay in the release of drug from the tablet might be due to formation of a more thick gel layer around the matrix of Acacia gum which was also observed during swelling process in the dissolution study at the end of 8 hours. During dissolution study it was observed that the tablets released the drug from matrix after considerable swelling. The order of percent release of drug (at the end of 8 h) was found to be MTX1> MTX2 > MTX3 > MTX4. All the formulations showed a matrix diffusion dependent release and this was confirmed due to linear relationship between the percent drug release and square root of time (Higuchi plots). In Higuchi plot 'r' value was 0.99.

Conclusion

The physio-chemical investigation showed that triple- layered aceclofenac matrix tablet prepared with Acacia gum showed better solubility and dissolution profile. Thus, it can be concluded that matrix tablet prepared with Acacia gum may be of potential use for improving bio availability and for reducing the GI toxicity of the drug. Matrix tablet may also be developed for other NSAIDS with poor solubility and GI side effect.

REFERENCES

Abrahim, M.A. Shirwaikar, A. 1997. Formulation of multi-layered sustained release tablet using insoluble bi-layer system. *Int. J. Pharm.,* 59(3); 161-167.

Aulton, ME.2007. The Design and Manufacture of Medicines. Church Hill Living Stone 3: 483-94.

Basak S.C., Reddy Jayakumar, Mani Lucas K.P. 2006. Formulation and release behavior of sustained release ambroxol hydrochloride HPMC matrix tablet. *Indian J. Pharm Sci.,* 68:594-8.

Bechgaard, H. Nielson, GH, Controlled release multiple units and single unit dosage. *Drug Dev Ind. Pharm.,* 1978; 4:53-67.

Conte, U. and Maggi, L. 1996. Modulation of the dissolution profiles from Geomatrix® multi-layer matrix tablets containing drugs of different solubility. *Biomaterials*, 17: 889–896.

Corner Anna, Piccalilli, Iselau Frida. Influence of different types of polymer on release mechanism of hydrophilic matrix tablet. *Molecules*, 2009:14(8), 230-241.

Derle D.V., Kasliwal N.H. and Chavan N. 2008. Development and comparative evaluation of xanthium gum and guar gum based sustained release matrix tablets of tizanidinessss hydrochloride. *Indian Drugs*, 45:485-89.

Deshmukh V.N. 2009. Development and evaluation of sustained release matrix tablet using hydrophilic gums as release modifier. *Journal of Pharmaceuticals Research,* 2(2):326-330.

Deshmukh V.N. 2009. Development and evaluation of sustained release matrix tablet using hydrophilic gums as release modifier. *Journal of Pharmaceuticals Research,* 2(2):326-330.

Dhopeshwarkar, V. and Zatj, J.L. 1993. Evaluation of Acacia Gum in the Preparation of Sustained Release Matrix Tablets, *Drug Develop Ind Pharm*., 19: 999-1017.

El-Nabarawi, M.A. 2005. Modulation of tenoxicam release from hydrophilic matrix: Modulator membrane versus rate-controlling membrane. Chem Pharm Bull 53**:**1083–7.

Garg G., Saraf Swaralata and Saraf, S. The pain management of Aceclofenac. Sciencedirect.com.

Ghosh, S. and Barik, B.B., Preparation and evaluation of aceclofenac sustained release formulation and comparison of formulated and marketed product. *Int J Medicine Med Sci.,* 2009; 1:375-382.

Gowda, D.V., Girish, B. and Shivakumar, H. 2008. Preparation and evaluation of carnauba wax microspheres' loaded with aceclofenac for controlled release. *Indian J Pharm Educ Res*., 42: 329-336.

Hayashi, T., Formulation study and drug release mechanism of a new theophylline sustained-release preparation. *Int J Pharm*., 2005; 304:91-101.

Hemnani, M. Patel, U. Patel, G. Daslaniya, D. Shah, A. Bhimani, B., Matrix tablets a tool of controlled drug delievery. *American J Pharm Tech Res.,* 2011;1:127-43

Higuchi T. 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. *J Pharm Sci.,* 50:874–875.

Higuchi, T., Rate of release of medicaments from ointment bases containing drugs in suspension. *International J Pharm Sci*., 1951; 50:874–875.

Hiten A. Panchal, Ajay K Tiwari. Formulation, development and In-vitro evaluation of bilayer tablets of glibenclamide as immediate release and sustained release. *Int J Pharm Sci and Health Care*, 2012; 2(4):1-18.

Hosny, EA. Oral extended drug delievery systems: a review. *Int J Pharm*., 1996; 133:149-53.

Hosseinali Tabandeh, Seyed Alireza Mortazavi *et al*. 2007. Preparation of Sustained-Release Matrix Tablets of Aspirin with Ethyl cellulose, Eudragit RS100 and Eudragit S100 and Studying the Release Profiles and their Sensitivity to Tablet Hardness. *Journal of Controlled Release,* 50(1):274-296

Huang, X., Brazel, C.S. 2001. On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. *J. Control. Rel.,* 73:121-136.

Jain sourabh, S.K. Yadav, and Patil. U.K. 2008. Preparation and Evaluation of Sustained Release Matrix Tablet of Furosemide using Natural Polymers. *Research J. Pharm. and Tech*., 1(4), 15-22.

Jantzen, GM. Robinson, JR., Sustained and controlled-release drug delivery systems, in Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, Third Edition, Revised and Expanded, Drugs and the Pharmaceutical Sciences, Marcell Dekker, Inc. New York, 1995: 575-609.

Kamboj Sunil, Gupta G.D. and Oberoy. Matrix tablet: An important tool for oral controlled –release dosage forms 2009:7 (published online www.sciencedirect.com)

Khan, G. M. 2001. Review, Controlled Release Oral Dosage Forms: Some Recent Advances in Matrix Type Drug Delivery Systems. Sciencesdirect.com. 1(5): 350-354.

Kothari, LP. Katariya, TR. Shah, PV. Somwanshi, SV.Lukkad, HR., Formulation and evaluation of once-daily sustained release aceclofenac sterculia urens gum matrix tablets. *Int J Novel Drug Deliv Tech*., 2011;4:142-48.

Krishnaiah, Y.S.R., Karthikeyan, R.S. and Satyanarayana, V. 2002. A three layered Acacia gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartarate. *Int J Pharm*., 241: 353-66.

Kumar, A.P. Kumar, D., Development and evaluation of controlled release matrix tablet of Acyclovir. *Der Pharmacia Lettre*, 5(2):347-353.

Kumar, R. Patil., S. 2010; Characterization of Aceclofenac Mouth dissolved Tablets. The present formulation using citric acid –heat treated Sodium bicarbonate for better reaction properties. *Scholara Research Library*, 2(1)220-236.

Lachman, L., Herbert, A. and Liberman, J. 1990. In: The Theory and Practice of Industrial Pharmacy, Varghese publishing House, Hind Rajasthan Building DadarMumbai-400001, 3rd Edn. p.318.

Lichtenberger, L.M., Wang, Z.M., Romero, J.J., Ulloa, C., Perez, J.C., Giraud, M.N. and Barreto, J.C. 1995. Non steroidal anti-inflammatory drugs (NSAIDs) associate with zwitterionic phospholipids: Insight into the mechanism and reversal of NSAID-induced gastrointestinal injury. *Nature,* Med 11:154-58.

Maggi, L., Bruni, R. and Conte, U. 2000. High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage forms. *Int J Pharm.,* 195: 229–38.

Mohammad Safqul Islam, Md. Mizanur Rahman Moghal*et al*., Effect of physiochemical on the release profile of ditiazem Hcl and naproxen from HPMC and kollidon SR based matrix tablet. *Indian J. Pharm. Educ*., 2009, 43:46-53.

Mutalik S., Usha A.N., K. Manoj*et al*., Preparation and in vitro evaluation of once daily sustained release tablet of aceclofenac. ijpsjournal.com. 2006.

Pornsak, Gary R. Development of multi-layered matrix tablet of Tramolol Hcl. (published online www.sciencedirect. com) 1998

Prajapati S.T., Patel L.D. and Patel D.M. 2009. Studies on formulation and in vitro evaluation of floating matrix tablet of domperidone. *Indian J. Pharm Sci.,* 71:19-23.

Robinson J. R. and Lee V. H. L. 1987. Controlled Drug Delivery Fundamentals and Applications, Vol. 29, 2nd Edn. Marcel Dekker, INC, New York and Basel: 4-6.

Sahebrao Kishor, Kulkarni V. Mohan. 2008. Formulation and in-vitro evaluation of dextrin matrix tablet of Ibuprofen for colon specific drug delivery. *Pak. J. Pharma Sci.*, 21(1): 17-20

Salsa, T., Veiga, F. and Pinna, M.E. 1997. Oral controlled release dosage forms. I. Cellulose ether polymers in hydrophilic matrices. *Ind. Pharm.,* 23: 929-38.

Semalty, M., Bisht, T. and Semalty, A. 2012. Study of tripe layered aceclofenac matrix tablet formulated using xanthum gum and guar gum. *International journal of Pharmaceutical Sciences and Nanotechnology,* 5(1):1621-26.

Siahi, M.R., Jalali, M.B., Monajjemzadeh, F., Ghaffari, F. and Azarmi, S. 2005. Design and evaluation of 1- and 3-layer matrices of verapamil hydrochloride for sustaining its release. *AAPS PharmSciTech*., 6(4):626-32.

Syed, I.A., Sri, S.P., Reddy, S. Kalamata V.N. and Yamani M.R. 2009. Modulating the release of diclofenac sodium matrix cores layered with hydrooxypropyl cellulose, hydrooxypropyl methylcellulose and sodium carboxyl methyl cellulose. *Indian Drugs*, 46:301- 09.

Tapia, V. Corbalán, E. Costa, and M. N. Gai *et al***.** Study of the Release Mechanism of Ditiazem Hydrochloride from Matrices Based on Chitosan−Alginate and Chitosan−Carrageenan Mixtures. *Biomolecules*, 2005, 6(5): 2389-2395.

Thapa, P. and Ghimire M. 2005. Effect of drug solubility and polymer viscosity on in vitro drug release from HPMC matrix tablet. *Indian Drugs*, 42:389-91.

Thomas Quinten, Yves Gonnissen. Development of injection molded matrix tablets based on mixtures of ethyl cellulose and low-substituted hydroxypropylcellulose. Science direct.com. 2009;37(4):207-216.

Winching Zhao, Lijun Song, Hongzhu Deng, Hue Yao. Hydration, Erosion, and Release Behavior of Guar-Based Hydrophilic Matrix Tablets Containing Total Alkaloids of Sophora alopecuroides. Drug development and industrial Pharmacy. 2009;35(5)594-602.

Zou, Meijuan, Wang Yue, Wax-Matrix Tablet for Time-Dependent Colon-Specific Delivery System of Sophora Flavescens Aiton: Preparation and In Vivo Evaluation. *Informa Healthcare*, 2009; 35(2):224-233.

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