Research article

Formulation and Evaluation of Taste masked Fast Dissolving Tablets of Ondansetron Hcl

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Abstract

During the last decade, the demand for mouth dissolving tablets has been growing, especially for geriatric and pediatric patients because of swallowing difficulties. Ondansetron Hcl as the model drug is a serotonin receptor (5-HT3) antagonist used in the prevention of chemotherapy induced nausea and vomiting. In this present study, the bitter taste of Ondansetron Hcl was masked using drug: Indion 204 in different ratios (1:1–1:3) and drug: eudragit E 100 in different ratios (1:1–1:4). For taste masking the ratio of drug: Indion 204 and drug: eudragit E 100 were optimized to 1:2 and 1:4 respectively by time intensity method. The FTIR studies showed drug and carrier were compatible. These were then compressed into tablets by direct compression method with using different superdisintegrants like Indion 414 in 1%, 1.5% and 2% concentration and croscarmellose sodium in 2%, 3% and 4% concentration. All formulations were evaluated for disintegration time, wetting time, weight variation, percentage friability and in vitro dissolution rate. Formulations with 2% Indion 414 and drug: Indion 204 in 1:2 ratio (DR6) and with 2% Indion 414 and drug: eudragit E 100 in 1:4 ratio (DE6) showed the disintegration time 10 seconds, 15 seconds and wetting time 30 seconds, 33 seconds respectively. In vitro dissolution studies of both formulations showed more than 90% drug released within 15 minutes. In vitro release profile, disintegration time and wetting time were remaining unchanged after two months when stored at 250C / 60% RH and at 400C / 75% RH.

Key words: Fast dissolving tablets, in-vitro disintegration time, wetting time, Ondansetron HCL.

Introduction

Patients often experience inconvenience in swallowing conventional tablets when water is not available. Furthermore, patients who have swallowing problems encounter difficulties in taking tablets [1], particularly pediatric and geriatric patients. Such problems can be resolved by means of mouth disintegrating tablet. This tablet disintegrates instantaneously when put on tongue, releasing the drug, which dissolves or disperses in the saliva[2]. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[3].

Ondansetron hydrochloride is a 5-HT3-receptor antagonist used as anti-emetic in conditions like motion sickness. In cancer chemotherapy, drug induced nausea and vomiting may occur so regularly that anticipatory vomiting occurs when patients return for treatment before the chemotherapeutic agent is given. If not controlled, the discomfort associate with drug induced emesis may cause a patient to refuse further chemotherapy. In this condition ondansetron hydrochloride is a drug of choice[4].The main criteria for mouth dissolving tablets is to disintegrate or dissolve rapidly in oral cavity with saliva in 15 sec to 60 sec, without need of water and should have pleasant mouthfeel [5]. It has been reported that ondansetron hydrochloride possess bitter taste hence the primary objective is to mask the bitter taste and further developing the drug into mouth dissolving tablets.

Materials and methods

Ondansetron Hcl, Indion 204, Indion 414 , Eudragit E

100, Croscarmellose sodium ,Avicel 101, Perteck-M, Aspartame, Pineapple flavor, Magnesium stearate, Aerosil are supplied by Lincoln Pharmaceuticals Ltd., Ahmedabad .

Formulation of FDTs of Ondestron HCL: Indion 204 AND Ondestron Hcl: Eudragit E 100 by Direct compression Method

Formulation

Mouth dissolving tablets of ondansetron Hcl: resin complex and ondansetron Hcl: eudragit E100 granules were prepared using direct compression method after incorporating different superdisintegrants such as INDION 414, croscarmellose sodium (Ac-Di-Sol) in different concentrations. Six formulations of each ondansetron Hcl: resin complex and ondansetron Hcl: eudragit E100 granules were prepared and each formulation contained one of the two superdisintegrants in different concentration. The methods of preparation, amount of resinates and drug: eudragit E 100 granules equivalent to drug, and other tabletting excipients were kept constant to avoid the influence of these on the results.Ondansetron Hcl resin complex (resinate) tablet containing 35.97mg resinate equivalent to 10mg of Ondansetron Hcl were prepared by using perteck–M, avicel PH 101, as directly compressible diluents, Ac-Di-Sol, INDION 414, were tried as a superdisintegrants. Resinate, perteck–M and avicel PH 101 were mixed in a glass mortar using a pestle. Superdisintegrants were incorporated in the powder mixture; aspartame (Sweetening agent), Flavor (Pineapple flavor), menthol were added to enhance the palatability of tablet and finally aerosil was added as lubricant. The mixture was weighed (125mg), die cavity of tablet machine was set for 125mg, and then tablet was compressed with 6mm flat punches using a Cadmach single punch tablet machine. By keeping weight of the tablet constant all the batches were prepared by direct compression method using single punch tablet machine at a fixed compression force. In the given formulations avicel 101 and perteck M®were used as directly compressible diluents. Perteck M® due to its negative heat of solution produces cooling sensations in the mouth while avicel 101 due to its high swelling index facilitates the rapid disintegration. Aspartame was selected as sweetening agent due to its intense sweetness. So it requires in very small quantity and it does not possess bitter after taste. Flavors are added to enhance the palatability of the preparation. Indion 414, croscarmellose sodium were used as a superdisintegrants due to its high swelling index and it requires in very small quantity for rapid disintegration of tablets.

In similar fashion the tablet of ondansetron Hcl eudragit E100 matrix (granules) were prepared containing drug eudragit E100 granules 52.08 mg, granules equivalent to 10mg of ondansetron Hcl.

Bitter taste was masked by,

i. complex with ion exchange resin - Indion 204.
ii. prepared granules with cationic polymer – Eudragit

TABLE 1: FORMULATIONS OF FDTs OF ONDANSETRON Hcl-INDION 204

Ingredients	DR1 [mg]	DR2 [mg]	DR3 [mg	DR4 [mg]	DR5 [mg]	DR6 [mg]
Resinate (Equivalent to 10mg of Ondansetron Hcl)	35.97	35.97	35.97	35.97	35.97	**35.97**
Perteck-M (Mannitol)	47.49	46.75	45.99	48.25	47.87	**47.50**
Avicel PH 101 (MCC)	31.67	31.16	30.67	32.16	31.92	**31.66**
Crosscarmellose Sodium	[Ac Di Sol]	2.5	3.75	5	-	- -
INDION 414	-	-	-	1.25	1.87	**2.5**
Aerosil	0.625	0.625	0.625	0.625	0.625	**0.625**
Aspartame	3.125	3.125	3.125	3.125	3.125	**3.125**
Menthol	0.5	0.5	0.5	0.5	0.5	**0.5**
Pineapple Flavor	3.12	3.12	3.12	3.12	3.12	**3.12**

TABLE 2 : FORMULATIONS OF FDTs OF ONDANSETRON Hcl-EUDRAGIT E 100

Ingredients	DE1 [mg]	DE2 [mg]	DE3 [mg]	DE4 [mg]	DE5 [mg]	DE6 [mg]
Granules (Equivalent to 10mg of Ondansetron Hcl)	52.88	52.08	52.08	52.08	52.08	**52.08**
Perteck-M (Mannitol)	37.04	37.09	36.34	38.59	38.21	**37.84**
Avicel PH 101(MCC)	25.21	24.71	24.21	25.71	25.47	**25.21**
Crosscarmellose Sodium [Ac Di Sol]	2.5	3.75	5	-	-	-
INDION 414	-	-	-	1.25	1.87	**2.5**
Aerosil	0.625	0.625	0.625	0.625	0.625	**0.625**
Aspartame	3.125	3.125	3.125	3.125	3.125	**3.125**
Menthol	0.5	0.5	0.5	0.5	0.5	**0.5**
Pineapple Flavor	3.12	3.12	3.12	3.12	3.12	**3.12**
Tablet Weight	125	125	125	125	125	**125**

TABLE 3: Comparison of D.T. AND W.T OF FDTs OF ONDANSETRON Hcl-INDION 204

Formulation	D.T. in sec	W.T in Sec
DR1	23 sec	42 sec.
DR2	18 sec	40 sec
DR3	12 sec	35 sec
DR4	18 sec.	40 sec
DR5	15 sec	38sec
DR6	**10sec**	**30 sec**

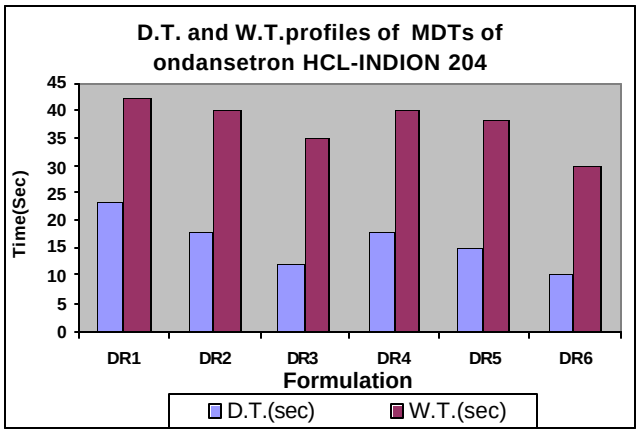
TABLE 4 : Comparison of D.T. AND W.T of MDTs of ONDANSETRON Hcl-Eudragi E 100

Formulation	D.T. in sec	W.T in Sec
DE1	25 sec.	44 sec
DE2	20 sec.	41 sec
DE3	18 sec.	35 sec
DE4	25 sec.	42 sec
DE5	20 sec.	40 sec
DE6	**15 sec.**	**33 sec**

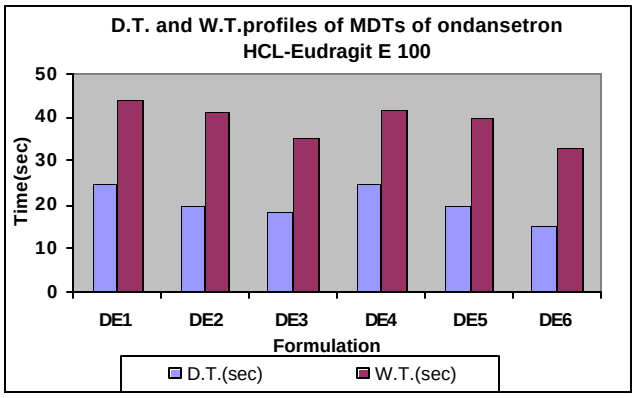
TABLE No. 5 : Dissolution Profiles of FDTs of ONDANSETRON Hcl-INDION 204

Formulation	% Release after 2.5min	% Release after 5min	% Release after 7.5min	% Release after 10min
DR1	60.71	72.31	84.15	94.78
DR2	65.28	75.52	86.1	95.53
DR3	73.12	82.71	91.03	98.79
DR4	67.39	78.1	87.31	96.03
DR5	72.11	80.15	89.31	98.13
DR6	**78.62**	**89.61**	**94.67**	**100.01**

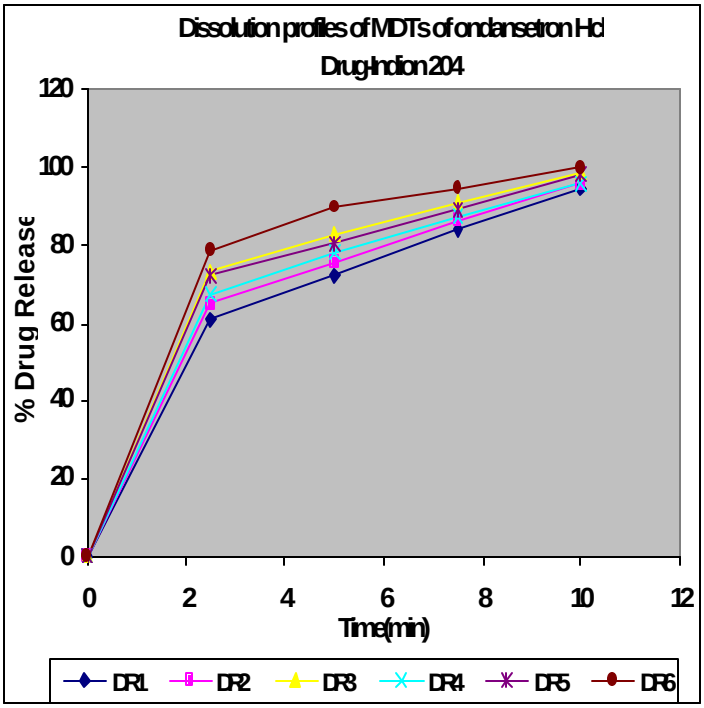
Graph no. 1 : Comparison of D.T. AND W.T OF FDTs OF ONDANSETRON Hcl-INDION 204



Graph no.2 Comparison of D.T. AND W.T of MDTs of ONDANSETRON Hcl-Eudragit E 100



Graph no. 3 Dissolution Profile of FDTs OF ONDANSETRON Hcl-INDION 204



Graph no. 4 Dissolution Profile of FDTs OF ONDANSETRON Hcl-EUDRAGIT E 100

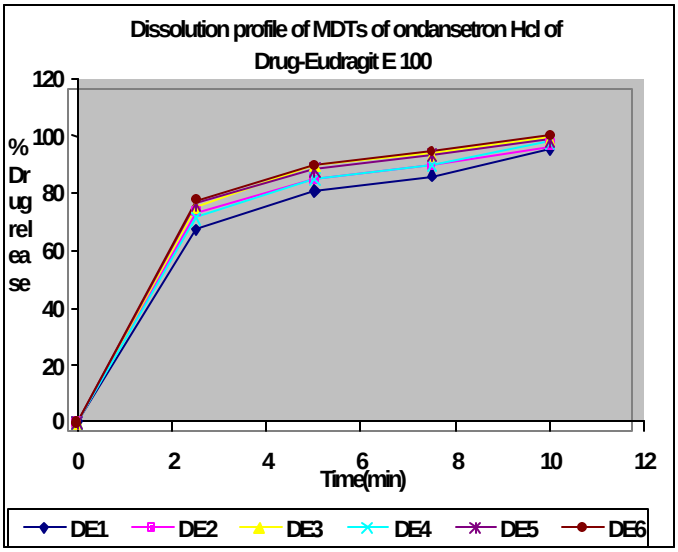


TABLE No.6 : Dissolution Profile of FDTs OF ONDANSETRON Hcl-EUDRAGIT E 100

Formulation	% Release after 2.5min	% Release after 5min	% Release after 7.5min	% Release after 10min
DE1	67.03	81.13	86.21	95.4
DE2	73.21	85.23	89.71	97.01
DE3	75.23	89.72	94.2	99.21
DE4	71.23	85.37	90.12	97.79
DE5	76.12	88.71	93.21	99.0
DE6	77.42	90	94.82	100.22

TABLE No.7 : Comparison of Formulated Tablets with Marketed Tablets

Parameters	Marketed Tablet	DR6	DE6
Hardness (Kg/cm^2)	4.0	4.0	3.8
Friability (%)	0.92	0.72	0.76
D.T. (sec.)	45	10	15
W.T. (sec.)	58	30	33

Results and Discussion

The present study was carried out to prepare ondansetron hydrochloride mouth dissolving tablets that can be used in the treatment of motion sickness. The bitter taste of Ondansetron HCl was masked by using weak acid cation exchange resin (INDION 204) and cationic polymer (Eudragit E 100). Mouth dissolving tablets can be prepared by **using direct compression method**.Direct compression method was carried out by using super disintegrants like INDION 414 in 1%, 1.5% and 2% concentration and croscarmellose sodium in 2%, 3% and 4% concentration. Six formulations (DR1 - DR6) were prepared by using drug resin (Indion – 204) complex and six formulations were prepared by using drug Eudragit E-100 granules.

The prepared tablets in all formulations possessed good mechanical strength with sufficient hardness and the values obtained lies between 3.6 - 4.0kg/cm^2. Percent friability was less than1% in the all formulations and the values obtained lies between 0.72 – 0.84%. All the tablets from each formulation passed weight variation test, as the percentage weight variation was within the pharmacopoeial limits. The thickness was almost uniform in all formulations and the values obtained were between 2.5 – 2.6 mm.

The disintegration time and wetting time for DR1–DR6 formulations were shown in table no. 3 and graph no. 1.The disintegration time and wetting time for DE_1 – DE_6 formulations were shown in table no. 4 and graph no. 2.In vitro dissolution profiles for DE_1 – DE_6 formulations were shown in table no. 6 and graph no. 4.The batch DR6 and DE6 were found to have disintegration time of 10 seconds and 15 seconds respectively. Hence batches DR6and DE6containing INDION 414 (2%) were chosen for further studies. The optimized formulations (DR6 and DE6) were then compared with the marketed tablet for disintegration time, wetting time, hardness friability. The results were shown in table no. 7. Stability studies were carried out at 25°C / 60% RH and 40° C / 75% RH for 2 months. Different parameters like disintegration time, hardness, friability and dissolution rate were evaluated. Both the formulations showed no significant variations in all the parameters and were found to be stable.

Summary and conclusion

Ondansetron Hcl is serotonine receptor ($5HT_3$) antagonist. It is an antiemetic drug. It is widely used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. It is also used for the prevention and treatment of postoperative nausea and vomiting.

Ondansetron is well absorbed from gastrointestinal tract and undergoes first pass metabolism. Ondansetron Hcl is bioavailable by oral route. It has a very bitter taste. Taste plays an important role in the patient acceptability as far as mouth dissolving/ dispersible tablets are concerned. Therefore the bitter taste of drug i.e. Ondansetron Hcl was successfully masked by the use of ion exchange resin and by use of eudragit E 100. In the present study the use of weak cation exchange resin INDION 204 was used.

Ion exchange resin and eudragit E100 were chosen for the taste masking of bitter drug due to the following reasons.

- Complete taste masking is possible.
- Economically affordable.
- Take minimum preparation time.
- Does not affect the bioavailability of the drug.
- The main rational for the formulation of mouth dissolving/ disintegrating tablet is as follows.
- It will be convenient for elderly patients and pediatric patients.
- It does not require water at the time of administration.
- Easy administration for bedridden patient.

The step-by-step studies were carried on to develop an acceptable taste masked mouth dissolving tablet.

Initially an appropriate grade of eudragit was selected. Eudragit E100 was selected for the taste masking of ondansetron Hcl. The taste-masked granules of drug and eudragit E100 were prepared by simple mass extrusion technique using syringe. The eudragit E100 and drug were mixed and ethanol was added in it to form a gel. This gel was then extruded from syringe to form a stringe. Ethanol was then evaporated. After complete evaporation of ethanol the stringe was crushed. These taste-masked granules were evaluated for taste and drug content was determined by U.V. Spectrophotometer at 248nm. The optimum drug eudragit E100 ratio was found to be 1:4.Dissolution studies indicate that the complete drug was released from the taste-masked granules of Drug: Eudragit E100 within 10 minutes in simulated gastric fluid pH 1.2. Initially an appropriate resin responsible for taste masking of drug was selected. The resin selected for the present work was INDION 204 a weak cation exchange carboxylic acid resin for taste masking purpose. Weak cation exchange resin was selected here because of its weak binding capacity and basic nature of Ondansetron Hcl; therefore it was selected for immediate release taste masking formulation. These resins were pretreated to remove organic and colored impurities. The moisture content of the resin was calculated and it was found to be in acceptable range. Resinate (drug: resin complex) was prepared by batch process and the drug content was determined by SHIMANDZU U.V. Spectrophotometer at 248nm. Prepared resinate was studied for the effect of pH and drug resin ratio. The optimum pH and drug resin ratio was found to be 4 and 1:2 respectively. Dissolution studies indicate that complete drug was released from resinate within 10 min. The physical properties like bulk density, angle of repose and the shape of resinate were found to be 0.7843g/cm^3, 27.54^0 and irregular respectively

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Mouth dissolving tablet of taste masked drug resin complex and drug eudragit E 100 granules were prepared using perteck-M (mannitol),avicel 101, aspartame, pineapple flavor, menthol, aerosil and different superdisintegrants.

Six formulations each of drug eudragit E100 granules (DE1-DE6) and drug resin complex (DR1-DR6) were prepared by varying the concentration of superdisintegrant and keeping other excipients constant. Formulations DR1 to DR3 and DE1 to DE3 were prepared by using Croscarmellose sodium in 2%, 3%, and 4% concentration. Formulations DR4 to DR6 and DE4 to DE6 were prepared by using INDION 414 in 1%, 1.5% and 2% concentration. Tablet weight was kept constant i.e. 125 mg.

The batch DR6 and DE6 were found to have disintegration time of 10 seconds and 15 seconds respectively.

Hence batches DR6and DE6containing INDION 414 (2%) were chosen for further studies. The optimized DR6 and DE6 formulations were evaluated for hardness, friability, weight variation, thickness, disintegration time, wetting time and dissolution study. The hardness, In vitro disintegration time, wetting time and friability of formulations DR6 & DE6 were found to be 4kg/cm^2, 10 seconds, 30 seconds, 0.72% and 3.8kg/cm^2, 15 Seconds, 33seconds, 0.76% respectively. All the tablet formulations passes weight variation test. The dissolution studies of both DR6 and DE6 tablet formulation showed that more than 90% of drug was released with in 7.5 minutes. The formulated tablet was then compared with the marketed tablet for disintegration time. The result showed that the formulated tablet disintegrated in 10-15 seconds as compared to 40-45 seconds for marketed ondansetron tablet (ZOFER MD). Stability studies were carried out at 25^{O}C / 60% RH and 40^O C / 75% RH for 2 months. Different parameters like disintegration time, hardness, friability and dissolution rate were evaluated. By observing the effect of storage and temperature on disintegration time, rate of dissolution, friability and hardness, it was confirmed that the formulated tablet posses good stability. Stability study results confirm that all parameters of prepared formulation remain unchanged It was concluded that the methods used for taste masking of bitter drug were found to be effective and mouth-dissolving tablet of the same passes all the pharmacopoeial standards. From above discussion it was concluded that the successful formation of tasteless mouth dissolving tablet of Ondansetron Hcl can be done by using INDION-414 than Croscarmellose sodium as a superdisintegrant. Thus an ideal bitterness' mouth dissolving / disintegrating Ondansetron Hcl tablets were prepared.

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Reference

1. Seager H.., Drug delivery products and zydis fast dissolving dosage form, *J. Pharm. Phamacol.*, 1998, 50, 375-382.
2. Renon J.P., Corveleyn S., Freeze-dried rapidly disintegrating tablets, *US Patent* No. 6,010,719, 2000.
3. Gregory G. k. E. and Hod, pharmaceutical dosage form package, *US patent*, 1981, 4, 305,502.
4. Kuchekar B.S., Badhan A.C.and Mahajan H.S. "Mouth Dissolving Tablets: A Novel Drug Delivery System", *Pharma Times*, 2003,35, Page-7-9
5. Wilson C.G., Washington N., Peach J., Murray G.R. and Kennerley J.; "The behavior of fast dissolving dosage form „ *Int. J. Pharm*., 1987,40, pp 119-123
6. Sunada, H.; *Powder Technology*; 122, pp 188-198 (2002)
7. European Directorate for Quality of Medicines (www.pheur.org.), *Pharmeuropa*, 1998, 10(4), 547
8. Indurwade N.H. , Rajyaguru T.H. and Nakhat P.D.; "Novel approach- Fast Dissolving Tablets", *Indian Drugs*, 2002,39(8), pp 405-409
9. Sastry S.V., Nyshadam J.R.and Fix J.A. " Recent technological advances in oral drug delivery- A Review", *Pharm. Sci.Tech.Today*, 2000, pp 138-144
10. Grother, L.P., et.al; "Taste masked fast dissolved freeze dried tablets" Cardinal Health, *Pharmaceutical Technology* and services.
11. Gregory G.K.E., Peach J.M. and Dumanya J.D., Articles for carrying chemicals, *US Patent* 4,371,516, 1983
12. Blank R.G., Mody D.S., Kenny R.J.and Aveson M.C., Fast dissolving dosage form *US Patent*,4, 946,684,1990
13. Vaskoik K.G. Solid pharmaceutical dosages in tablet triturate form and method of producing same, *US Patent* 5,082,667,1992
14. Sunada, H.; *J. Pharm. Sci.;* 88(10), pp 1004-1010 (1999)
15. Remon, J.P., Corveloyn, S. Freeze dried rapidly disintegrating tablets *US Patent* 6,010,719 (2000)
16. Dorfner , K. " *Ion Exchanger Properties and Ap-*

plications" Third Edition, An Arbor Science Publisher, 2, 1972

17. Jain, N.K.; "*Advances in controlled and Novel drug Delivery*", First Edition, pp 290-306, 2001

18. Martin, G.L., " *Ion Exchange and Adsorption Agents in Medicines"* Little Brown, Boston 1955.

19. Borodkin , S.Ion Exchange Resin Delivery system, In "*Polymers for controlled Drug Delivery (P.J. Tarcha, ed.) CRC Press*, Inc, Boca Raton, pp 215-230, 1991.

20. Format given by Ion Exchange India Ltd. Mumbai.

21. Borodkin, S; Sundber, D.P. US Patent 3594470 (1971).

22. *US Patent* 3152986 (1971).

23. Jain, N.K.; *Advances in controlled and novel drug delivery*; First edition pp 290 (2001).

24. Bruck, S.D.; *Controlled drug delivery*; Vol –I, pp 150-151.

25. Borodkin,S.; Yonker, M.H.; *Journal of pharmaceutical sciences*; 59(40), pp 481(1970).

26. Literature provided by Ion Exchange India, Mumbai.

27. Ion Exchange Resins and Sustained release; Swarbik,J.*;Encyclopedia of pharmaceutical Technology*, Vol-8, pp 203-217.

28. Mahesh Bhalekar, J.G.Avari and S.B. Jaiswal; "Cation Exchangers in pharmaceutical formulations." *Indian Journal of pharmaceutical Education*,38(4), Oct – Dec. 2004.

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