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Effect of Excipients on Oxcarbazepine Release from Modified Release Matrix Tablets

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ABSTRACT

The present investigation was undertaken with an objective of formulating modified release (MR) matrix tablets of Oxcarbazepine (OXC) an anti-epileptic drug, based on cellulose ether polymers like Hydroxy Propyl Methyl Cellulose (HPMC K4M and LVCR 100) and Hydroxy Propyl Cellulose (HPC JF) as drug release retardants to overcome poor patient compliance and exposure to high doses associated with currently marketed immediate release (IR) dosage forms. The tablets were prepared by direct compression process and evaluated for various physico- chemical/mechanical parameters. Among three polymers used, HPMC LVCR 100 is selected as release retardant based on the viscosity and gel formation during dissolution. The effect of different fillers like Avicel PH 101, Avicel PH 105, Pre gelatinized starch (PGS), maize starch with spray dried lactose (FLOWLAC) and Di-calcium phosphate (DCP) on OXC release was also studied and the OXC percent release at the end of 12h is in the order of DCP>FLOWLAC>Avicel PH 101>Avicel PH 105>PGS. Based on the dissolution data obtained with different fillers and keeping in view of the results from the pre compression studies, and gel layer retaining with the matrix tablets, Avicel PH 105 was selected as carrier to carry out further formulation development. Since, OXC is poorly water soluble drug, solubilizing agents like surfactants, cyclodextrins and polyethylene glycols were included in the formulations and their effect on OXC release was studied in order to achieve therapeutic effective levels. Formulations containing 20% (w/w) of Hydroxy Propyl-β-Cyclodextrin gave superior OXC release of $85.50 \pm 1.62\%$ at the end of 12hours and fulfils the regulatory requirement. The dissolution data was also evaluated for drug release kinetics and mechanisms.

Keywords: Oxcarbazepine, matrix tablets, cellulose ether polymers, fillers and solubilizing agents.

INTRODUCTION

Over the past few decades several new chemical entities (NCEs) have been discovered, out of which 40% are lipophilic and poorly soluble drugs (Mudith D 2011). Solubility of the drug is the main obstacle in the delivery of the NCEs and also existing drugs. The ability of improving the solubility and delivery of poorly soluble drugs is very important step in formulation development. It can be enhanced through either altering the macromolecular characteristics of the drug particles, or chemical or mechanical modification of the environment surrounding the drug molecule. Particle size reduction, addition of surfactant, pH adjustment, self-emulsifying systems and inclusion in cyclodextrin-drug complexes are the best examples for the solubility enhancement techniques (Mohanachandran, 2010).

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Together with the solubility, the permeability behaviour should also be considered in the development of formulation for oral administration. Drug absorption from solid dosage forms after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two steps, *in vitro* dissolution may be relevant to the prediction of *in vivo* performance.

OXC (as both mono therapy and adjunctive therapy) has shown efficacy in the treatment of partial onset seizures with epilepsy (Tripathi, 2010) and belongs to the category of BCS class II, and its dissolution is the rate-limiting step for absorption (Wellington, 2001). OXC is having half-life of 2h and is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite, which has a half-life of 9h. The maximum dose administered per day is 2400mg and administered 2-3 times in divided doses (Sean, 1999). Different dosage strengths like 150, 300 and 600mg of immediate release (IR) tablets are marketed. In the existing dosage form (as an IR tablet), poor patient compliance and exposure to high doses of the drug may be anticipated and modified release (MR) dosage forms are needed for better therapeutic efficacy and patient compliance. So far no reports were published on CR/MR dosage forms of OXC. However, some patents on OXC controlled release formulations were published (Bharat PM 2006, Sankar R 2007, Jayanta KM 2009, Padmanabh PB 2009). Hence, the present investigation was aimed to develop twice a day oral MR tablet dosage forms for OXC based on cellulose ether polymers like HPMC, HPC as drug release retardants. Since, OXC is poorly water-soluble drug, its release from the modified release tablets is incomplete and therapeutically effective drug levels may not be achieved. So, excipients like surfactants, cyclodextrins and polyethylene glycols were included in the formulations and their effect on the OXC release was studied in order to achieve therapeutically effective levels of OXC from MR tablets.

EXPERIMENTAL

Materials and Methods

OXC (Novartis India Ltd, Mumbai), Hydroxy Propyl Methyl Cellulose K 100 LV (Colorcon, India), Hydroxy Propyl Methyl Cellulose K4M (Colorcon, India), Hydroxyl Propyl Cellulose JF (Aqualon-Herculus, USA), Microcrystalline cellulose-Avicel PH 105 (FMC Biopolymers, USA), Microcrystalline cellulose- Avicel PH 101 (FMC Biopolymers, USA), Pregelatinized starch (Rouette Pharma, France), Maize starch with Spray dried lactose-FLOWLAC (Rouette Pharma, France), Dicalcium phosphate (Finar, Mumbai), Poly ethylene glycol 6000 (Merck Pvt Ltd, Mumbai), Beta Cyclodextrin (Rouette Pharma, France), Hydroxy Propyl Beta Cyclodextrin (Rouette Pharma, France), Sodium lauryl sulphate (Merck Pvt Ltd, Mumbai), Talc (Finar, Mumbai), Magnesium stearate (Finar, Mumbai) were used. All the chemicals and reagents are of analytical grade.

Analytical Procedures

Both UV-VIS spectrophotometric method and RP-HPLC methods were used in the present investigation. UV-VIS spectrophotometric method (UV-Double Beam Spectrophotometer, UV-1800, Shimadzu, Japan) based on the measurement of absorbance at 256nm in a methanol stock solution was used. A reverse phase HPLC system was used for the analysis of OXC in different samples. Chromatographic separation was performed on a Shimadzu Prominence HPLC system equipped with LC 10 AVP binary pumps, DGU 20A Degasser, M20 A PDA detector and LC 10ATVP auto sampler with 200 μ L loop volume. LC solution software was used to collect and process the data. Mobile phase consisting of 0.02% v/v formic acid: methanol (50:50%) at 1.0mL/min flow rate was used and the mobile phase was filtered through membrane filter (Millipore Nylon disc filter of 0.45 μ) and sonicated for 3 min in ultrasonic bath before use. Quantification and linearity were achieved at 229 nm over the concentration range of 10-50 μ g/mL and a Phenomenex C₁₈ column (150mm x4.6mm, 5.0 μ) was used and separation was carried out at ambient temperature with an injection volume of 10 μ L.

Solubility Studies

Excess amounts of OXC (50mg) was added to 15mL of each fluid in a 25mL stopper conical flask and the mixtures were shaken for 24 hours at room temperature ($28 \pm 1^\circ\text{C}$) on rotary shaker (Remi Rotary Shaker, India). After 24 hours of shaking 1mL aliquots were withdrawn at different time intervals and filtered immediately using a 0.45 μ nylon disc filter. The filtered samples were diluted suitably and assayed for OXC by above HPLC method. Shaking was continued until three consecutive estimations were same. The solubility experiments were run in triplicate.

Drug excipients compatibility by FT-IR spectroscopy

The FT-IR spectra of pure drug and OXC with different excipients like HPMC K4M, HPMC LVCR 100, HPC JF, Avicel PH 105, Avicel PH 101, PGS, FlowLac, DCP, SLS, PEG 6000, β -CD and HP- β - CD was measured using ATR-FTIR spectrophotometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm^{-1} at a resolution of 1.0 cm^{-1} . The powder or film sample is simply placed onto the ATR crystal and the sample spectrum is collected.

Preparation of OXC MR Tablets

OXC MR tablets were prepared by direct compression method, as per formulae given in Table 1. HPMC K4M, HPMC LVCR 100 and HPC-JF were used as release retardant materials. Sufficient quantities of MCC (Avicel PH 101 and PH 105), pregelatinized starch, maize starch and spray dried lactose and dicalcium phosphate were used to raise the bulk volume of the tablets to a weight of 400mg each. Talc and magnesium stearate at 0.5% w/w levels were used as glidant/lubricants. All the ingredients were passed through sieve # 80 before mixing. In case of PEG 6000 fraction of sieve# 100 was used.

Table 1: Formulae of MR tablets of OXC with different excipients.

Ingredients	Formulations (Amounts in mg)												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
OXC	150	150	150	150	150	150	150	150	150	150	150	150	150
HPMC K4M	80	-	-	-	-	-	-	-	-	-	-	-	-
HPMC LVCR 100	-	80	-	80	80	80	80	80	80	80	80	80	80
HPC JF	-	-	80	-	-	-	-	-	-	-	-	-	-
Avicel PH 105	166	166	166	-	-	-	-	126	126	106	86	106	86
DCP	-	-	-	-	-	-	166	-	-	-	-	-	-
Avicel PH 101	-	-	-	166	-	-	-	-	-	-	-	-	-
Pre gelatinized starch	-	-	-	-	166	-	-	-	-	-	-	-	-
FlowLac	-	-	-	-	-	166	-	-	-	-	-	-	-
SLS	-	-	-	-	-	-	-	40	-	-	-	-	-
PEG-6000	-	-	-	-	-	-	-	-	40	-	-	-	-
β-CD	-	-	-	-	-	-	-	-	-	60	80	-	-
HP-β-CD	-	-	-	-	-	-	-	-	-	-	-	60	80
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	400	400	400	400	400	400	400	400	400	400	400	400	400

Initially drug and polymers were mixed thoroughly and then required quantities of fillers were added and finally the blend was mixed with talc and mixed thoroughly for 5min in a poly bag and then added the required amount of magnesium stearate and mixed for another 5 min. Powder blends (for 50 tablets each) of all the above formulations were compressed on single punch tablet press (Cadmach, India) using 10 mm punches (round shape) to a hardness of 4-6 kg/cm².

Evaluation of Flow Properties of powder blend

The powder blends were evaluated for parameters like bulk density, tapped density, Carr's index, Angle of repose, and Hausner's ratio (United State Pharmacopoeia 2007).

Evaluation of OXC MR Tablets

The compressed MR tablets were evaluated for following properties: drug content, uniformity of weight, friability, hardness, and disintegration time and *in vitro* drug release profiles (Lachman, 1987).

Drug content

Ten tablets were weighed and powdered in a mortar. Accurately weighed tablet powder samples equivalent to 20mg of OXC was transferred to a 100mL volumetric flask, and the OXC was extracted into 75mL methanol and then finally the volume was made to 100 mL with methanol. This solution was filtered through 0.45μ nylon disc filter and the filtrate was suitably diluted with methanol and the samples were analyzed by HPLC. The estimations were carried out in triplicate.

Uniformity of weight of tablets

The individual and total weight of 20 tablets from each batch was determined. Percentage deviation of the individual weights from the average weights was calculated.

Hardness

The hardness of the tablets was measured with a Monsanto hardness tester (M/s Campbell Electronics, model EIC-

66, India). The results reported were average of 6 tablets for each formulation.

Friability

For each formulation 10 tablets were weighed, placed in Friabilator (M/S Cambell Electronics, India) and were subjected to 100 rotations in 4min. The tablets were reweighed and friability was calculated by the following formula:

$$Friability = \frac{W_2 - W_1}{W_1} \times 100$$

Where W₁ is the initial weight and W₂ is the final weight of the tablets.

In vitro Dissolution studies

In vitro dissolution studies of MR tablet formulations prepared were carried in 900 mL of 0.1N HCl with 0.25% w/v SLS as dissolution medium using USP XXI type II (Paddle method) Dissolution Rate Test Apparatus.(LABINDIA, DS 8000) at 50 rpm. The temperature was maintained constant at 37±0.5°C. 5 mL aliquots were withdrawn at different time intervals and filtered using a 0.45μ nylon disc filters and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted if necessary and assayed for OXC by HPLC method. The dissolution experiments were conducted in triplicate.

Release kinetics and mechanism

Different kinetic models i.e., zero-order (Brazel, 2000) first-order (Lapidus, 1966), Higuchi's (Higuchi, 1963), and release mechanism model Korsmeyer Peppas (Korsmeyer, 1983) were applied to interpret the release profile of OXC from matrix systems. Due to the differences in drug release kinetics, the Peppas constant k, though is one of the measures of release rate, should not be used for comparison. Therefore, to characterize the drug release rate in different formulations, mean dissolution time (MDT) was calculated from dissolution data using the formula: MDT = (n/n+1) × k^{-1/n}, where n is the release exponent and k is the Peppas constant (Mockel JE 1993). MDT value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the

polymer. A higher value of MDT indicates a higher drug retarding ability of the polymer and vice-versa (Hamzaha, 2010).

RESULTS AND DISCUSSION

OXC is not yet official in any pharmacopoeia; official dissolution rate test is not available. However, dissolution rate tests were reported where 0.1N HCl with 0.25% w/v SLS was used as dissolution medium for evaluating the *in vitro* dissolution profiles of IR OXC formulations (Nirav P 2008). Based on the published reports, the solubility of OXC in 0.1N HCl with 0.25% w/v SLS, 0.1N HCl with 0.5% w/v SLS, 0.1N HCl with 1% w/v SLS and distilled water were carried out and the results were shown in Figure 1. An increase in SLS concentration increased the OXC solubility in 0.1N HCl. A 3.32-fold increase in OXC solubility with 0.5% w/v SLS in 0.1N HCl was observed when compared to without SLS and the solubility of OXC increased with increasing the SLS concentration. Based on the data of the solubility studies and keeping in view of the discriminating power of the selected dissolution medium and excipients selected in the formulation development studies all the dissolution experiments were carried out in 0.1N HCl with 0.25% w/v SLS as dissolution medium.

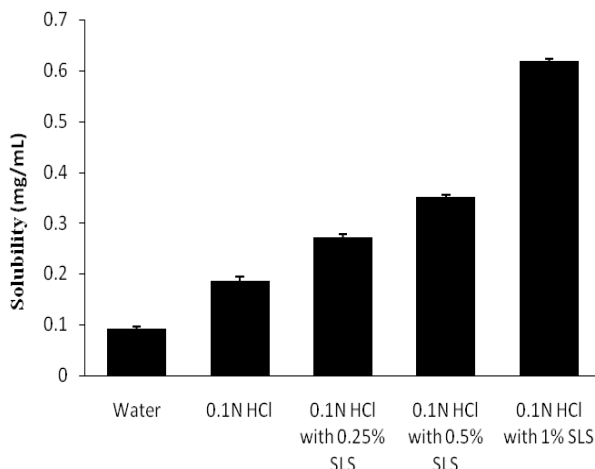


Fig. 1: Solubility of OXC in different fluids.

Drug excipient compatibility study

FTIR studies were carried with a view to evaluate the *in situ* drug and excipient/s compatibility. Figure 2 shows the IR spectra of pure OXC and OXC with different excipients. Pure OXC showed characteristic IR absorption bands at 3334 cm^{-1} for the N-H group bending, 1645 cm^{-1} for the C=O stretching. The absorption bands at 1556 cm^{-1} were denoted for stretching vibrations of C=C in aromatic ring. These characteristic IR absorption bands of OXC were all retained in the presence of the selected excipients indicates that there is no interaction between the OXC and excipients.

Determination of pre and post compression parameters

The results of various pre compression parameters are given in Table 2. These results indicate that the powder blends of all formulations are suitable to prepare tablets by direct

compression technique. The compressed tablets fulfilled the official compendial requirements regarding drug content, uniformity of weight, hardness and friability. The results are given in Table 3.

In Vitro Dissolution Studies

All the tablet formulations were subjected to *in vitro* drug release studies using 0.1N HCl with 0.25% w/v SLS as dissolution medium, in order to assess drug release profiles including release kinetics and drug release mechanisms from tablets. In the present investigation swellable polymers like HPMC K4M, HPMC LVCR 100 and HPC-JF were used to retard the OXC release from the MR tablets.

Initial formulation studies were carried out to look in to the release retarding effect of different swellable polymers like HPMC K4M, HPMC LVCR 100 and HPC JF at a level of 20%w/w in the formulations (F1-F3) using AVICEL PH 105 as filler. The release profiles were shown in Figure 3. All the polymers gave a controlled release pattern over a period of 12h, as these polymers swelled upon contact with the dissolution media and a gel layer was formed on their surface. This gel layer retarded further ingress of fluid and subsequent drug release. F1 containing OXC and HPMC K4M released lesser amount of drug (29.66 ± 1.01) at the end of 12h. This low percent of drug release is due to the higher viscosity of the polymer. F2 containing OXC and HPMC LVCR 100 released an amount of 48.87 ± 2.10 at the end of 12h, whereas, the F3 gave 67.76 ± 3.10 OXC release at the end of 12h. However, with the F3 containing HPC JF as release retardant material, no gel layer was formed but the tablets were slowly and completely eroded at the end of 12h. A good gel layer was observed with the F1 and F2 and the more swelling was observed with the F2 containing HPMC LVCR 100 and is because of low viscosity of the polymer and is a good candidate as a drug release retardant for poorly water soluble drugs like OXC. Based on these results and on MDT values (Table 4) obtained, and the solubility of the OXC, the studies were further carried out using HPMC LVCR 100 as a release retardant material.

Diluents fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. Diluents slightly affect the drug release from dosage form. Among the various water soluble and insoluble and directly compressible grade diluents, few diluents such as, AVICEL PH 101 and 105, PGS, maize starch with spray dried lactose (FLOWLAC) and DCP were used in studies to further formulate MR matrix tablets and their effect on OXC release was studied. F4-F7 were developed using AVICEL PH 101, PGS, FLOWLAC (maize starch with spray dried lactose) and DCP respectively. The comparative OXC release profiles were shown in Figure 4. F4 containing AVICEL PH 101 as filler gave 54.78 ± 3.30 percent drug release at the end of 12h and is higher than the AVICEL PH 105 (F2). Initial burst release at 1 h is 11.31 ± 1.15 and 6.78 ± 1.12 respectively for F4 and F2. Superior burst release was achieved with F4 containing AVICEL PH 101 as filler. This could be due to the quicker swelling of the formulation when compared to F2. Further trials

were carried out using PGS as filler (F5) and the release profile was shown in Figure 4. The percent release at the end of the 12h is 38.87 ± 4.01 . The slower drug release observed with pre gelatinized starch is may be due to the increased viscosity of gel layer and decreased penetration of dissolution medium towards the matrix core. This result was further confirmed by the higher MDT value of 461.93 min (Table 4). While, the formulation (F6) containing water soluble filler maize starch with spray dried lactose showed higher release of $66.39 \pm 2.12\%$ at the end of 12h. The increase in release is may be due to solubility of filler in the dissolution medium and thereby making channels in gel matrix. This also leads to deformation of the matrix shape in the dissolution medium and results the erosion of matrix in dissolution medium. Further, DCP was used as filler (F7) and resulted in $71.73 \pm 3.03\%$ release at the end of 12h. The release profiles were shown in Figure 4. This higher release of OXC is may be due to the erosion of the tablet in the dissolution medium. Hence, based on the dissolution data obtained with F4-F7 and keeping in view of the results from the pre compression studies, and gel layer retaining with the matrix tablets the Avicel PH 105 was selected to carry out the further formulation development.

Since, OXC is poorly water-soluble drug, its release from the MR tablets is incomplete and therapeutically effective drug levels may not be achieved for a MR dosage form. The obtained drug release profiles with F1-F7 explain this fact i.e. only between 29-71% of OXC release was obtained with all these formulations. Hence, excipients in the category of solubilizing agents, like surfactants (SLS), complex forming agents (cyclodextrin like β -CD and HP- β -CD) and solubilizing and channeling agents (PEG 6000) at levels of 10-20% w/w of the total tablet weight were included in the formulations and their effect on the OXC release was studied in order to achieve therapeutically effective levels of OXC.

Surfactants are commonly used in pharmaceutical dosage forms as wetting agents. SLS is an anionic and water-soluble surface active agent. It can be used effectively as a wetting agent in both alkaline and acidic conditions. SLS has been used in

quantities of 10% w/w of total tablet weight for its surface tension lowering capability and to improve dissolution of poorly soluble drugs like OXC. Formulation containing SLS 10% (F8) showed $72.39 \pm 4.32\%$ release at the end of 12h and the increase in OXC release is may be due to enhancement of wettability of OXC by the SLS there by solubility within the matrix gel. The release profiles were shown in Figure 5. In another trial PEG 6000 at 10% w/w total tablet weight was incorporated in the formula (F9) and a good drug release ($80.98 \pm 1.65\%$) was observed with formulation containing PEG 6000 at the end of 12h. Increase in drug release is due to the solubilizing effect of PEG 6000 on OXC within the matrix gel and also the channeling effect by PEG within the matrix gel, there by more diffusion of solubilized OXC from the core. The release profiles were shown in Figure 5. Further formulations were developed with cyclodextrins at levels of 15% and 20% w/w of the total tablet weight (F10, F11, F12, and F13). Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a hydrophobic central cavity. In aqueous solutions, cyclodextrins can form inclusion complexes with lipophilic drugs by entrapping the non polar part of it inside the hydrophobic cavity. A $79.67 \pm 2.85\%$ and $84.18 \pm 1.14\%$ OXC release was observed with F10 and F11 containing β -CD at 15 and 20% w/w levels respectively at the end of the 12h. The release profiles were shown in Figure 5. An $82.27 \pm 0.73\%$ and $85.50 \pm 1.62\%$ OXC release was observed with F12 and F13 containing HP- β -CD at 15 and 20% w/w levels respectively at the end of the 12h. The release profiles were shown in Figure 5.

Overall, increase in the cyclodextrins levels increased the OXC release from the tablets. The OXC release was more with HP- β -CD when compared to the β -CD. This is because of the more hydrophilic nature of HP- β -CD than the β -CD. Among the all the formulations, F13 containing 20% w/w HP- β -CD gave superior and required OXC release of $85.50 \pm 1.62\%$ at the end of 12h and fulfils the regulatory requirements in terms of percent drug release (i.e. not less than 85% at the end of the time points for modified release dosage forms).

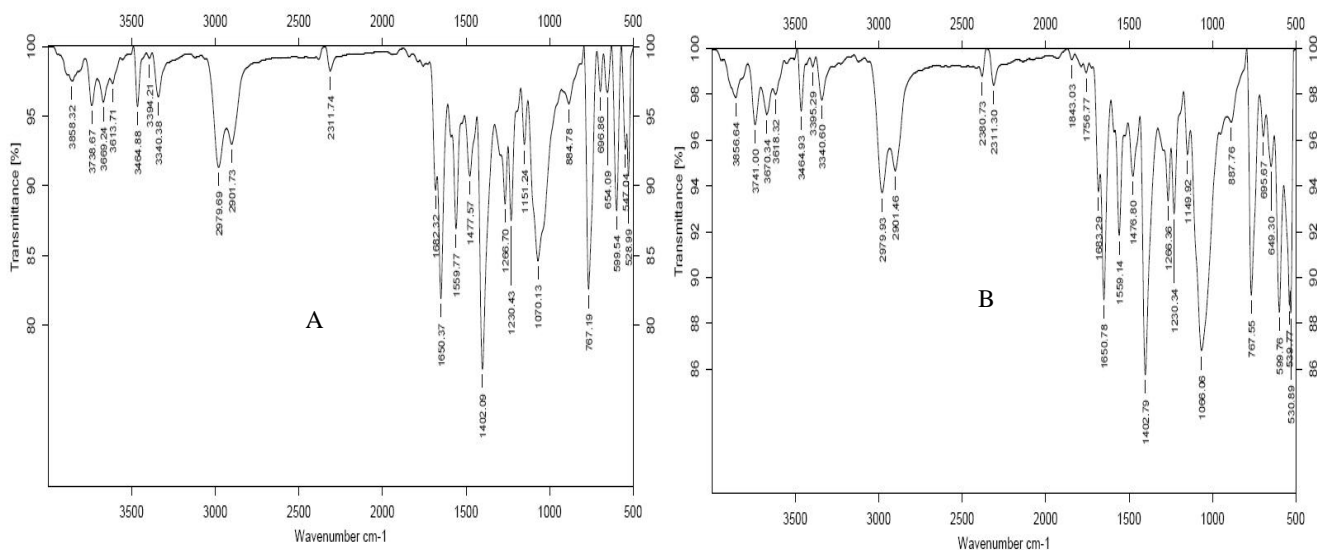


Fig. 2: continues....

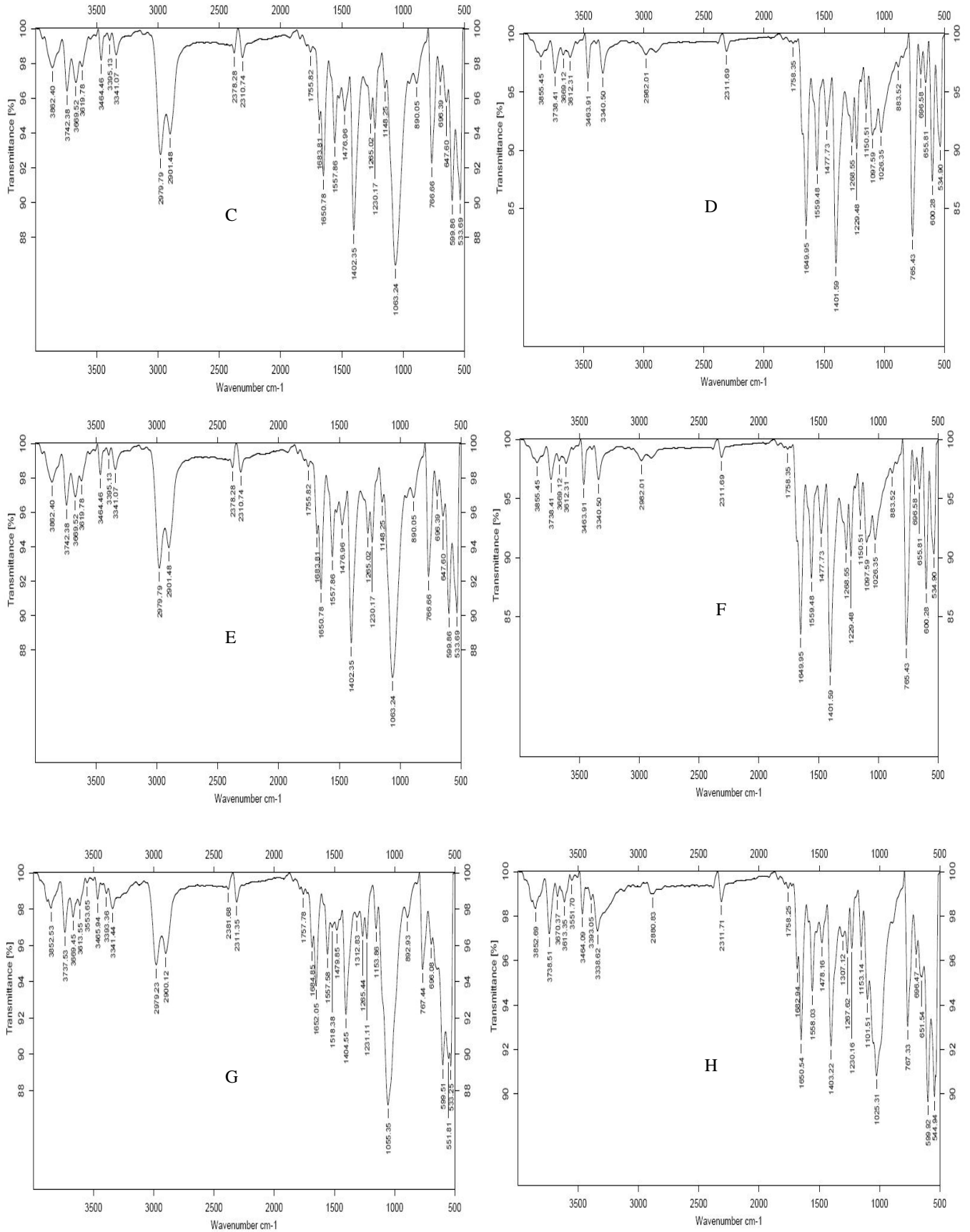


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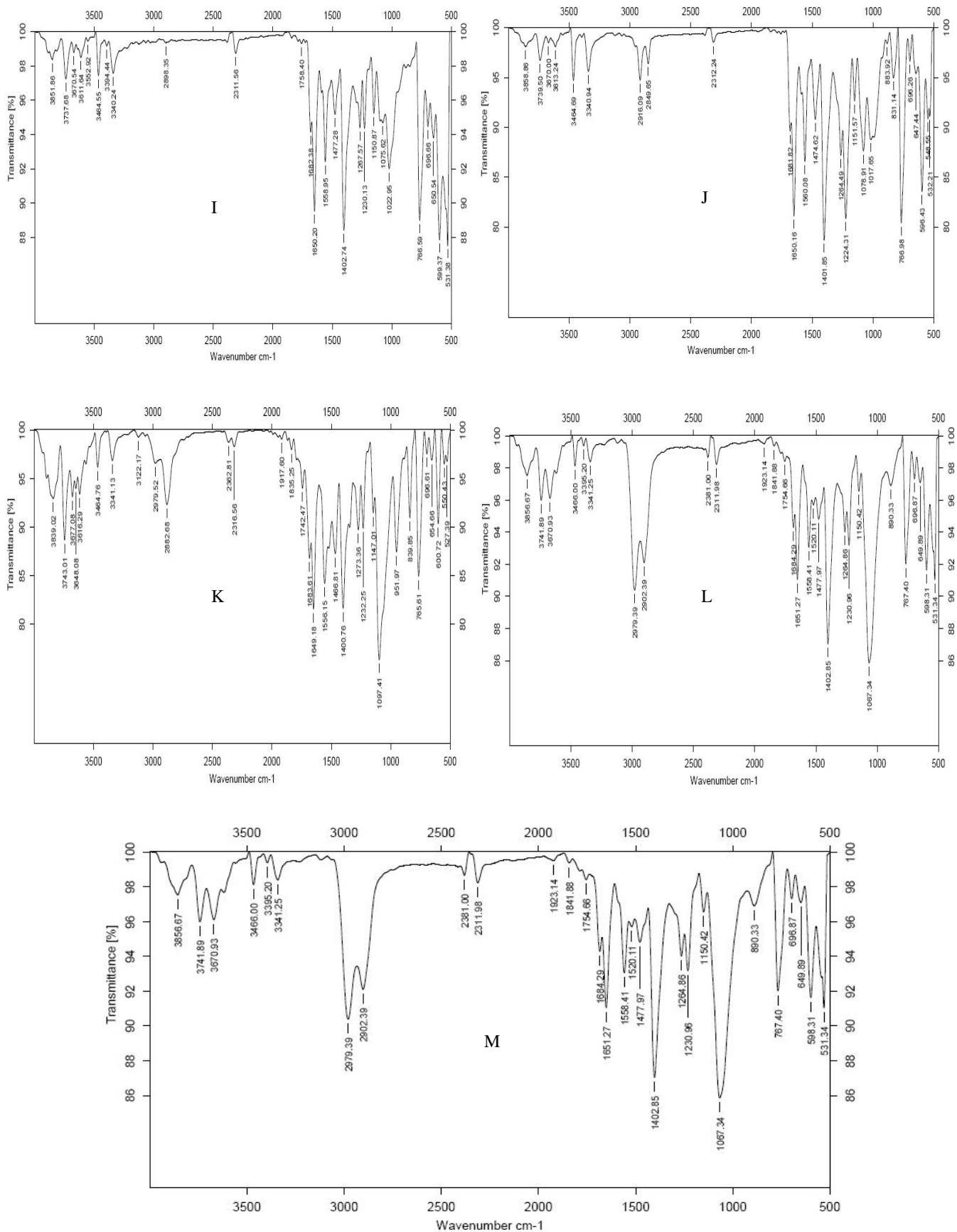


Fig. 2: FTIR spectra of (A) pure OXC, (B) OXC-HPMC K4M, (C) OXC-HPMC LVCR 100, (D) OXC-HPC JF, (E) OXC-Avicel PH105, (F) OXC-Avicel PH101(G) OXC- PGS (H) OXC-FLOWLAC (I) OXC-DCP (J) OXC- SLS, (K) OXC- PEG 6000, (L) OXC-β-CD, (M) OXC-HP- β-CD.

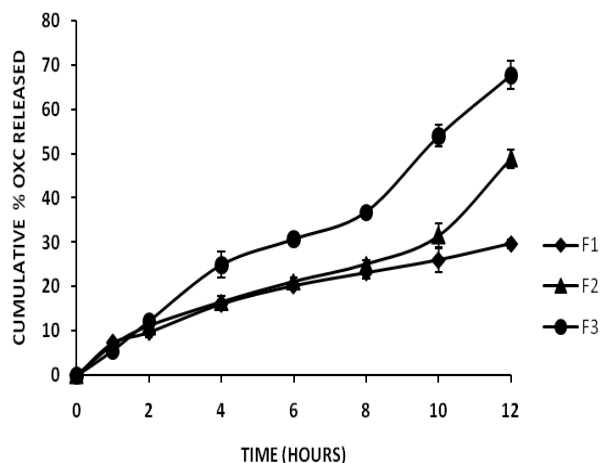


Fig. 3: Comparative dissolution profiles of F1-F3

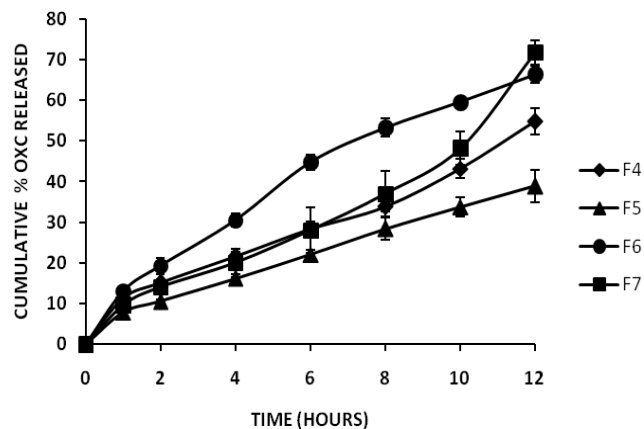


Fig. 4: Comparative dissolution profiles of F4-F7

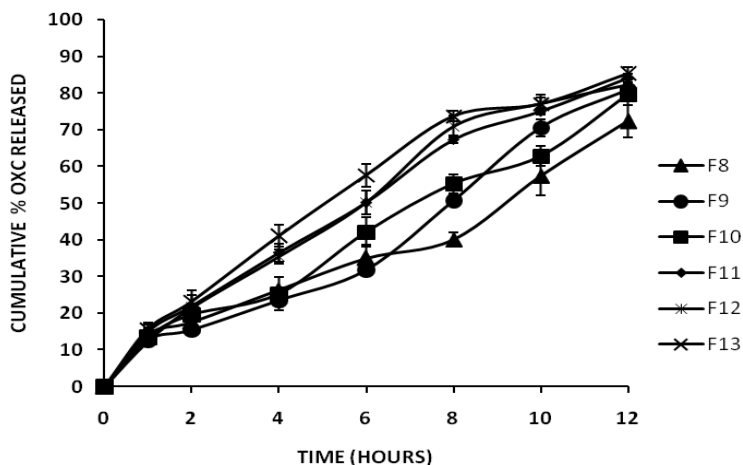


Fig. 5: Comparative dissolution profiles of F8-F13

Table 2: Pre compression parameters of tablet powder blend.

Formulation	Bulk density (g/mL)	Tapped density (g/mL)	Compressibility index (%)	Hausner ratio	Angle of repose (°)
F1	0.336	0.252	33.3	1.33	28.6
F2	0.331	0.257	28.7	1.34	27.5
F3	0.399	0.258	42.9	1.39	34.2
F4	0.319	0.233	41.2	1.36	31.1
F5	0.329	0.243	35.3	1.35	30.5
F6	0.345	0.262	31.6	1.31	28.1
F7	0.342	0.249	37.3	1.37	27.9
F8	0.353	0.256	37.8	1.37	29.8
F9	0.339	0.253	33.9	1.33	30.4
F10	0.332	0.251	32.2	1.32	29.5
F11	0.319	0.248	28.6	1.28	30.5
F12	0.324	0.254	27.5	1.27	28.3
F13	0.325	0.251	29.4	1.29	29.9

Table 3: Various evaluation parameters of OXC MR tablets.

Formulation	Drug content (mg/tab)	Weight variation (mean ± SD)	Hardness (kg/cm ²)	Friability (% wt. loss)
F1	149.2	398 ± 2.4	5	0.62
F2	149.8	398 ± 3.2	5	0.52
F3	151.4	399 ± 1.2	5	0.56
F4	150.3	399 ± 2.4	5	0.41
F5	149.4	401 ± 2.3	5.5	0.69
F6	150.6	402 ± 2.1	5	0.52
F7	149.2	398 ± 2.2	5.5	0.57
F8	149.2	397 ± 3.2	4.5	0.71
F9	150.8	398 ± 2.9	5	0.59
F10	149.4	397 ± 1.6	5	0.51
F11	149.1	398 ± 1.8	4.5	0.66
F12	148.9	398 ± 1.9	5	0.72
F13	149.5	403 ± 2.1	5	0.54

Table 4. Release kinetic parameters for OXC MR formulations

Formulations	Zero order		First order		Higuchi		Peppas		MDT (min)
	K ₀	R ²	K	R ²	K _H	R ²	n	R ²	
F1	2.26	0.948	0.025	0.967	4.13	0.996	0.576	0.992	543.60
F2	3.42	0.947	0.046	0.905	14.50	0.876	0.713	0.962	422.00
F3	5.34	0.983	0.085	0.935	23.57	0.941	0.959	0.987	490.00
F4	4.02	0.976	0.058	0.964	16.52	0.938	0.610	0.969	309.78
F5	3.05	0.987	0.368	0.994	12.76	0.977	0.640	0.983	461.93
F6	5.37	0.969	0.875	0.996	22.45	0.993	0.683	0.994	293.00
F7	5.30	0.947	0.090	0.834	22.81	0.853	0.757	0.941	312.43
F8	5.33	0.971	0.092	0.916	22.16	0.907	0.579	0.957	222.21
F9	6.09	0.924	0.117	0.823	26.13	0.807	0.719	0.852	257.40
F10	6.37	0.946	0.122	0.952	27.19	0.946	0.662	0.939	235.95
F11	6.89	0.981	0.147	0.983	29.22	0.987	0.716	0.990	246.23
F12	7.08	0.962	0.159	0.994	29.98	0.988	0.734	0.992	261.82
F13	6.88	0.960	0.143	0.992	29.37	0.990	0.803	0.999	286.87

Drug release kinetics and mechanisms

The R² values for F1, F5, F6, F10-13 obtained with first order plots were found to be superior when compared to the R² values obtained with zero order plots. These results indicating that the OXC release from F1, F5, F6, and F10-13 followed first order kinetics (Table 4).

In case of F2, F3, F4, F7, F8, and F9 the R² values obtained with zero order plots were found to be superior when compared to the R² values obtained with first order plots. These results indicating that the OXC release from F2, F3, F4, F7, F8, and F9 followed zero order kinetics. The Higuchi square root model showed higher correlation coefficient values (0.807-0.996) and diffusion is the release mechanism for OXC from the tablets.

The graphs of Log % Qt versus log t showed a linear relationship with R² values ranged from 0.852-0.999 and 'n' values from 0.57-0.80 and indicates anomalous transport is the release mechanism except with the F3 where 'n' value is 0.95, indicates the super case II transport.

Formulations containing different excipients from F8-F13 gave 'n' values in the range of 0.5-0.8 indicates the drug release mechanism with these formulation is because of swelling and diffusion (anomalous transport). OXC release profiles of these formulations confirm this fact.

CONCLUSIONS

Overall, HPMC LVCR 100 at 20% w/w level as release retardant polymer and AVICEL PH105 as filler (F2) was selected as core formulation and in the absence of HP-β-CD, F2 gave 48.87 ± 2.10 % OXC release at the end of 12h and with 20% w/w HP-β-CD gave superior and required OXC release of 85.50 ± 1.62 % at the end of 12h and fulfill the regulatory requirements in terms of percent drug release.

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