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Monolithic Osmotic System Of Lornoxicam Using Amorphous Ternary Cyclodextrin Complex As A Core

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Abstract: The aim of the present investigation was to develop Monolithic Osmotic Tablet System (MOTS) of pH dependent and poorly water soluble lornoxicam (LOR) for controlled drug release. MOTS of LOR comprised freeze dried ternary amorphous complex of drug as core and cellulose acetate with pore former as release controlling membrane. LOR has a poor water (61 µg/ml) and pH dependant (3 µg/ml in pH 1.2) solubility. Freeze dried amorphous ternary complex of drug containing β-cyclodextrin and arginine (LOR:β-CD:Arg) in stoichiometry ratio of 1:1:1 was found to give 30 fold and 300 fold increase in solubility of LOR in water and in 1.2 pH buffer respectively as compared to plane drug which is prerequisite for MOTS. Amorphization of LOR was confirmed by XRD, DSC and SEM study. LOR has a half-life of 3-4 hr which necessitates developing controlled release system of drug for longer period of time. Different formulation variables like type of polyethylene oxide, concentration of pore former, coating weight gain, concentration of osmotic agent and aperture diameter were optimized to achieve zero order drug release. Optimized MOTS of LOR was found to be delivering drug at controlled zero order rate up to 24 hr. pH independent controlled drug release behaviour was revealed by carrying out dissolution in 1.2 pH, 4.5 pH and 6.8 pH dissolution medium. Hence, the developed monolithic osmotic system of LOR utilizing freeze dried amorphous ternary complex was found to be promising approach for controlled release of pH dependent and poorly water soluble drug candidates.
Keywords: Lornoxicam, ternary complex, monolithic osmotic system, controlled release, polyethylene oxide.

Introduction

Conventional preparation is generally administered two or three times a day, which will lead to large fluctuation in drug plasma concentration and side effects on human body. Constant plasma level can offer a therapeutic advantage for many drugs in terms of both efficacy and tolerance of the treatment.[1] Hence once-daily controlled release preparation is often desirable which can be attained by various systems based on diffusion, dissolution and osmotic mechanism.[2]

Osmotically controlled drug delivery offers many advantages such as pH and gastric motility independent drug release as well as delivery of drugs by zero order release kinetics. In addition, it holds a prominent place among

controlled release systems having many advantages like reducing risk of adverse reactions, improving patient compliance and exhibiting comparable in vitro/in vivo drug release.[3]

In the 1970s, scientist first introduced the elementary osmotic pump (EOP) [4] and brought forward its basic theory. However, EOP is only suitable for the water soluble drugs. To overcome this limitation, two-compartment[5], two-layer push–pull[6] and three-layer osmotic tablets systems[7] were developed. However, all of these osmotic tablet systems have a common disadvantage of using sophisticated technology of complicated side identification which should be employed to ensure the orifice drilled on the surface of the drug layer after coating. To overcome the side identification technique, sandwiched osmotic pump tablet system was developed but it has disadvantage in respect of more number of formulation steps [8]to avoid additional production procedures and develop economical system, the research was shifted towards development of Monolithic Osmotic Tablet System (MOTS).

MOT system consists of a core tablet coated by semipermeable membrane with a micro-orifice drilled on the tablet surface. This technology was found to be simple, economical and easily scalable in preparation which could deliver water-soluble drugs at an approximately constant rate up to 24 h. However, it was not feasible for the delivery of drugs with low solubility as these drugs dissolved insufficiently and settled at the bottom of the tablet.[9] In order to troubleshoot this problem, attempts were made to enhance the solubility of the drugs [10,11]and to modify the performance of the semipermeable membrane.[12,13]But these approaches were limited only for a few kind of drugs and found to be incapable for drugs which has pH dependant solubility. To overcome this limitation, efforts were taken for the delivery of low solubility drugs by improving drug released rate and increasing drug solubility. One of the approaches to overcome pH independent solubility problem is to convert them into ionic substance by reacting with or adding alkali/acid.[14]However, this method can only apply to a few drugs with special chemical structures. Okimoto et al. used (SBE)7m-β-CD as a solubilizer and osmotic agent to prepare MOTS for poorly water insoluble drug such as testosterone.[15] But such approach was ineffective for drugs having both water-insolubility and pH dependant solubility.

Lornoxicam (LOR) belongs to class of non-steroidal anti-inflammatory drugs. It is chemically(6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide-1,1-dioxide).[16,17] Lornoxicam is a peculiar example of drug which has got poor water and pH dependant solubility. Our previous work reports that amorphous freeze dried ternary complex of LOR:β-CD:Arg in 1:1:1 stoichiometric ratio found to give very drastic increase in the solubility of drug[14].

In this research work, we are utilizing solubility enhancement characteristic of freeze dried ternary complex of LOR:β-CD:Arg as core for development of osmotic drug delivery system. Cellulose acetate with pore former is utilized as coating layer which acts as drug release rate controlling membrane.

The aims were:

1.To develop tablet core containing LOR with enhanced water and pH independent solubility.

2.To study the effects of tablet core variables, including type of polyethylene oxide and their combinations and sodium chloride (NaCl) amount as well as coating variables like percent coating weight gain, concentration of pore former and orifice size to propose an delivery mechanism and the optimal core formulation of MOTS.

Materials and Methods

Material

Lornoxicam (LOR) was procured from Sun Pharmaceutical, Vadodara, India. B-cyclodextrin (β-CD) was procured from Wacker-Chemie GmbH, Germany. Arginine was purchased from SD Fine Chemicals, India. Different grades of Polyethylene oxide (PolyoxTM) were procured from Colorcon India. Cellulose acetate (39.8% acetyl content and 3000 molecular number) was purchased from Sigma–Aldrich India. Polyethylene glycol 400 (PEG 400) was obtained from Merck India Ltd. Other excipients like Lactose anhydrous (DCL21), Microcrystalline cellulose (MCC PH101), Ac-Di-Sol (SD-711), Colloidal silicon dioxide (Aerosil 200) and Magnesium Stearate were supplied by Signet Chemical Corporation, India. The other chemicals used were of analytical grade.

Methods

Phase solubility and saturation solubility study of complex

Phase solubility studies experiment was performed by the method reported by Higuchi and Connors.[18,19] In brief, an excess amount of LOR was added to the solutions containing various concentrations of β-CD (0–10 mM) prepared in purified water and in pH 1.2 buffer. The solutions were shaken for 24 h at 370C on rotating shaker (water bath shaker, Remi, India) at 200 rpm for the period of 48 hr. The equilibrated aliquots were filtered through 0.22 µm PVDF filter (Millipore, India) followed by dilution and analyzed spectrophotometrically at 376 nm (Jasco V-530 UV/Vis Spectrophotometer). The stability constant Ks for 1:1 LOR-β-CD were calculated, using the equation 1.

$$Ks(1:1) = \frac{slope}{S_0(1-slope)} \quad (1)$$

Where, S_0 is the solubility of the Lornoxicam in the absence of β-CD.

Preparation of solid complexes

Freeze drying

Solid-state LOR ternary complexes with β-CD and arginine in 1:1:1 M ratio was prepared using freeze drying technique. Drug and β-CD were accurately weighed and dissolved in distilled water (10 ml). To this aqueous solution accurately weighed quantity of arginine was added as a ternary agent. This solution was stirred on magnetic stirrer for 1 h in order to completely dissolve the LOR. The resulting solution was freeze dried. Pre-freezing of samples was done at –70°C for 24 hr, and then the flasks were connected to freeze-drier (Labconco, USA) under vacuum (1 mbar, –30°C). The dried powder was passed through 80 mesh sieve and stored in a desiccator until further evaluation.

Physical Mixture

Equal mole amounts of LOR, β-CD and arginine (1:1:1) were mixed thoroughly in the dry state. The mixture was passed through 60# and stored in desiccator.

Saturation Solubility

Saturation solubility studies were performed in water and in 1.2 pH buffer described by Higuchi and Connors.[19] Excess of pure LOR and prepared solid freeze dried ternary complex were added to 10 mL of distilled water and in 1.2 pH buffer in a screw-cap tube and shaken in a rotary flask shaker at room temperature (25°C) for 24 hrs. The resultant suspension was treated at 37^{o}C with 100 rpm in incubator shaker. After 24 hr. samples were withdrawn and filtered through 0.22 µm PVDF filter and analyzed spectrophotometrically. Experiment was performed in triplicate.

Characterization of the freeze dried complex

Differential scanning calorimetry

Thermal characteristics of plane LOR and its complexes were done under dry nitrogen purge (20 ml/min) at a heating rate of 10 °C/min using a Differential Scanning Calorimeter (Perkin Elmer, Pyris-6 DSC, USA).

Powder X-ray diffractometry

Powder X-ray diffraction patterns of plane LOR and its solid complexes were recorded using Phillips P Analytical X'Pert PRO powder X-ray diffractometer using Ni-filtered, Cu Kα radiation, a voltage of 40 kα and a current of 30 mA. The scanning rate employed was 2 °/min and samples were analyzed between 2θ angles of over 10–40^{0}C.

Preparation monolithic osmotic tablet of LOR utilizing ternary freeze dried complex

Optimized ternary freeze dried complex of LOR was used for the preparation of monolithic osmotic tablet as shown in Table 1. Solid amorphous freeze dried ternary complex of LOR was mixed with different excipients

like microcrystalline cellulose, anhydrous lactose and polyethylene oxide which previously passed through 40# sieve. After ensuring thorough mixing, blend was granulated by using polyvinylpyrrolidone K30 as binder with isopropyl alcohol. The resulting mixture was passed through 22# sieve and then granules were air dried at 40^0C for 3 hr. Sodium chloride and colloidal silicon dioxide (AEROSIL® 200 Pharma) were added extra-granularly followed by lubrication with magnesium stearate. The resultant mixtures were compressed into core tablet using 9.5 mm standard concave punches on 16 station rotary tablet machine (Cadmach, India) at a hardness 4-5 kg/cm^2.

Coating and drilling

Core tablets were coated using a conventional coating pan with diameter 220 mm (Bombay Machine, Mumbai, India). Cellulose acetate (CA, 3% w/v) in acetone: water (95:5) mixture containing polyethylene glycol 400 (PEG-400) as plasticizer was used as a coating solution. Initially, tablets were preheated by passing hot air through the tablet bed and by rotating the pan at a lower speed of 6-8 rpm. Coating process was started with a rotation speed of 12–14 rpm. The spray rate and atomizing air pressure were 5-7 mL/min and 1.80 kg/cm2 respectively. The inlet and outlet air temperature were 40^oC and 35^oC, respectively. Samples were taken off with particular interval, weighed and the process was continued till the desired weight gain was achieved. Curing of tablets was carried out in a forced air oven (Hot Air Oven AI-900,Best engineering, India) at 40^oC for 1 hr. The coated tablets were stored at room temperature for 24 hr before an orifice was drilled by a microdriller on either side of the tablets.

Effect of different formulation variables

The composition of different core formulations with composition of coating layer is listed in Table 1. Effect of different process and excipients formulation variables like different mol. wt. of PEO and their combination, % of pore former, effect of percent coating weight gain, percent of osmotic agent and drilled aperture diameter on release rate was studied. Optimization of these parameters will play a crucial role in attaining the desired drug release profile. Effect of concentration of different molecular weight of polyethylene oxide (PEO) and their combination on in vitro drug release was studied. Initially PEO WSR N80 (mol.wt. 200000), PEO WSR 750 (mol. wt. 300000), PEO WSR 205 (mol.wt. 600000) and PEO WSR 1105 (mol.wt. 90000) at 30 % w/w concentration was used as shown in table 1 and later on their combination of low mol. wt. PEO WSR N80 and somewhat high mol.wt. PEO WSR1105 was tried in varying concentration. Effect of coating weight gain by using cellulose acetate as semipermeable membrane and Sodium Chloride (NaCl) as an osmotic agent was studied. PEG 400 was used as pore former with varying aperture diameter (0.6. 0.8 and 1.0 mm). Effect of varying concentration of osmotic agent (NaCl) at 20 %, 30% and 40% and effect of pore former (PEG-400) levels with respect to (EC, v/w) of 10.0%, 20.0% and 30.0% ,Per cent coating weight gain of CA at 5%, 7% and 9% , effect of aperture diameter (F15) were studied and optimized. All these formulation factors were varied to study their effect on in vitro release of the drug to achieve the desired zero order release up to 24 hr. Optimization of these parameters will play a crucial role in attaining the desired drug release profile the amount of plasticizer and membrane thickness of different formulations variables are listed in Table 1.

In vitro release test

In vitro dissolution testing was performed in a paddle apparatus (USP type II; TDT-08 L; Electrolab Mumbai) for dissolution study of LOR MOTS. Tablets were placed in 900 mL of pH 6.8 phosphate buffer using sinker. The dissolution was carried out at a paddle rotation speed of 75 rpm at 37± 0.5^0C. Samples were withdrawn at different intervals, filtered through 0.45µm cellulose acetate filter (Millipore), and immediately analyzed using UV spectrophotometer (Zasco, Japan) at λmax of 376 nm. Samples were taken at 2, 3, 4, 6, 9, 12, 18 and 24 hr. The mean of six determinations was used to calculate percent drug released for each Formulation (F).

Effect of hydrodynamic force on drug release profile

To check the in vivo reliability of the formulation with respect to hydrodynamic conditions of the GIT, in vitro release studies were performed for six samples at various rotational speeds in USP-II (Paddle) type dissolution apparatus. Phosphate buffer (pH 6.8) was used as dissolution media (pre-equilibrated to 37 ± 0.5^0C). Samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45µm nylon membrane filter.

Effect of different pH medium on drug release profile

To assure a reliable performance of the developed formulations, the in vitro release studies were conducted for six samples in media of different pH using USP- II dissolution apparatus. The release media were water,

hydrochloric acid (pH 1.2) and phosphate buffer (pH 6.8). Samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45µ nylon membrane filter.

Kinetics of drug release

The drug release kinetics of optimized batch of LOR MOTS formulation was performed for different models by using Microsoft Excel Add-Ins DD Solver[3]. The correlation of coefficient was taken into consideration to evaluate best model fit of the drug release from the optimized formulation.

Results and Discussion

Phase solubility and saturation solubility study

Phase solubility study gives an idea about the stoichiometric ratio between cyclodextrin to drug. It was observed that there is linear increase in solubility of LOR with respect to increase in concentrations of β-CD in pH1.2 buffer as shown in Figure 1. On the other hand, the phase solubility curve in water showed negative deviation indicating very less increase in solubility of complex which may be attributed to precipitation of LOR. Increasing amounts of β-CD increased the amount of LOR solubility into pH 1.2 improving the aqueous solubility of LOR in acidic buffer media. The stability constants (Ks) for the complexes at 37^0C, assuming a 1:1 stoichiometry, calculated from the slope of phase solubility diagram were 100 M-1 for β-CD-LOR in simulated gastric fluid pH 1.2. Assuming a 1:2 stoichiometry in water, the stability constant found 229 M^{-1} which indicated a suitable and stable complex formation.

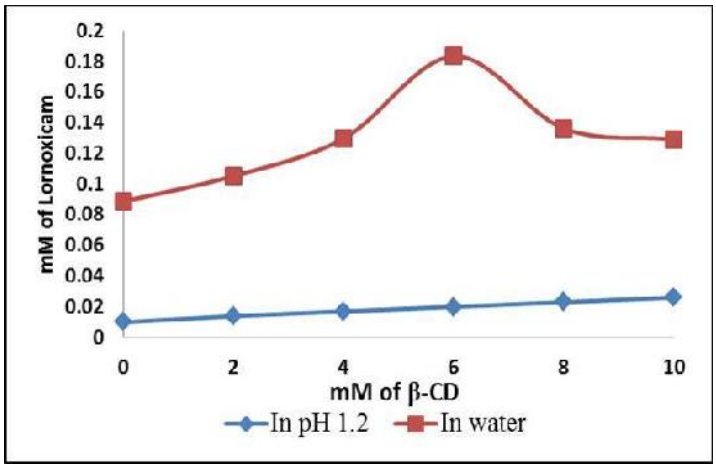

Figure 1: Phase solubility of LOR:β-CD:Arg freeze dried ternary complex

Saturation solubility of freeze dried ternary solid complex as compared to plain LOR in water and pH 1.2 buffers is **shown in Figure 2.** From the data, we conclude that the freeze dried ternary complex showed significant improvement (30 times in water and 300 times in pH 1.2 buffer) in solubility of LOR as compared to plain drug. This is because of highly amorphous nature of freeze dried inclusion complex, and the basic micoenvirmental pH generated by presence of alkalizer (arginine) as ternary component play an important role which add on significant effect in improving solubility of LOR. This is in agreement with the reported literature.[18,12]

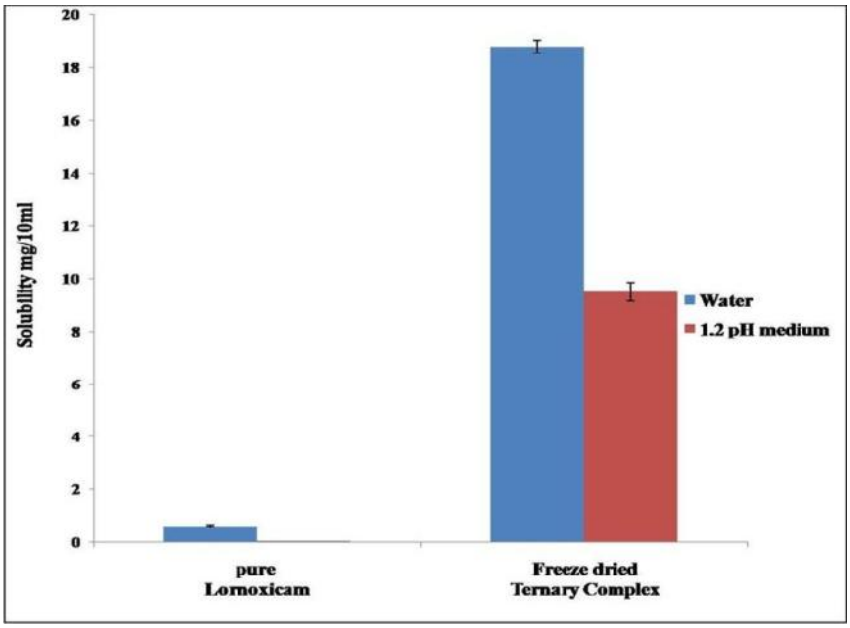

Figure 2: Saturation solubility of Lornoxicam and freeze dried ternary complex in water and in pH 1.2 buffer

Differential scanning calorimetry

Thermal behaviour of LOR, β-CD, arginine, LOR: β-CD:Arg physical mixture and LOR: β-CD:Arg freeze dried ternary complex are shown in Figure 3**.** LOR showed a sharp exotherm at 226.86 ^{0}C which signifies the melting point of drug. In case of β-CD, the initial broad endotherm peak at 102.07^{0}C revealed the moisture loss from the cyclodextrin. The arginine showed three characteristics peak in the thermogram corresponding to moisture loss (99.18 ^{0}C), melting endotherm at (218.18^{0}C) and decomposition endotherm (244.79 ^{0}C).Thermograms of the LOR:β-CD:Arg physical mixture showed a slight shift in the exothermic peak of the LOR at 209.58^{0}C while the LOR:β-CD:Arg freeze dried ternary inclusion complex showed a significant shift in the exotherm of the LOR which appeared at 181.45^{0}C. Lower shift in exothermic peak of LOR is attributed to the presence of ternary mixture, as the melting point of a material is known to shift to the lower scale in the presence of other substances.[20] Hence significant lower shift in case of freeze dried ternary complex was attributed to amorphization of drug with β-CD due to homogeneous inclusion complex formation.

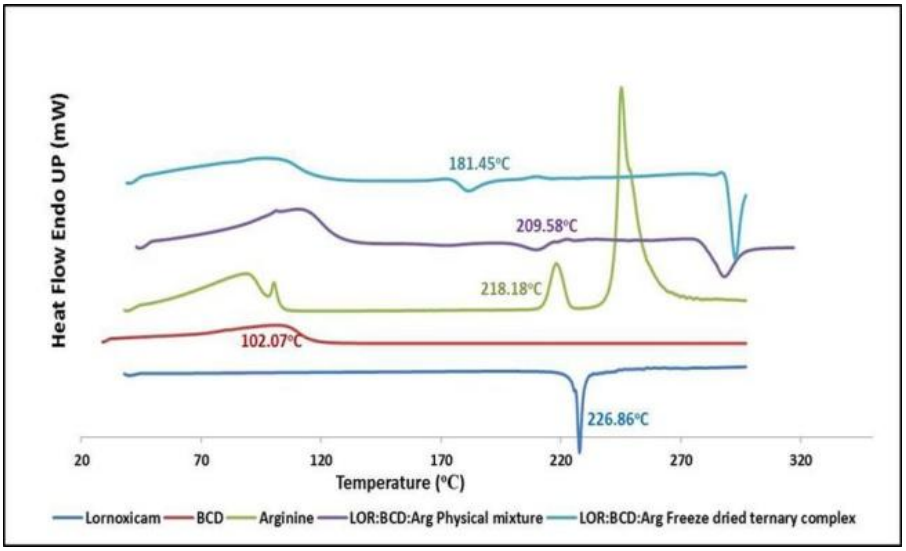

Figure 3: DSC thermograms of LOR, β-CD, Arginine, LOR:β-CD:Arg Physical mixture and LOR:β-CD:Arg ternary freeze dried complex

Powder X-ray diffractometry (PXRD)

The PXRD patterns of pure LOR, β-CD, Arginine and freeze dried ternary complex are presented in Figure 4. The diffractogram of LOR exhibited a series of intense peaks at 11.9, 13.78, 15.66, 21.3 and 31.8 which are indicative of crystalline character of pure LOR. β-CD and arginine also showed characteristic crystalline peaks in their respective diffractograms. But in case of freeze dried ternary complex, a significant reduction in peak intensity of the crystalline peaks of the ternary components was observed. The results signify that ternary complex formation of LOR with β-CD and arginine cause complete amorphization of the solid complex. Thus, these observations are in accordance with the reported literature[21,22] supporting the DSC observations.

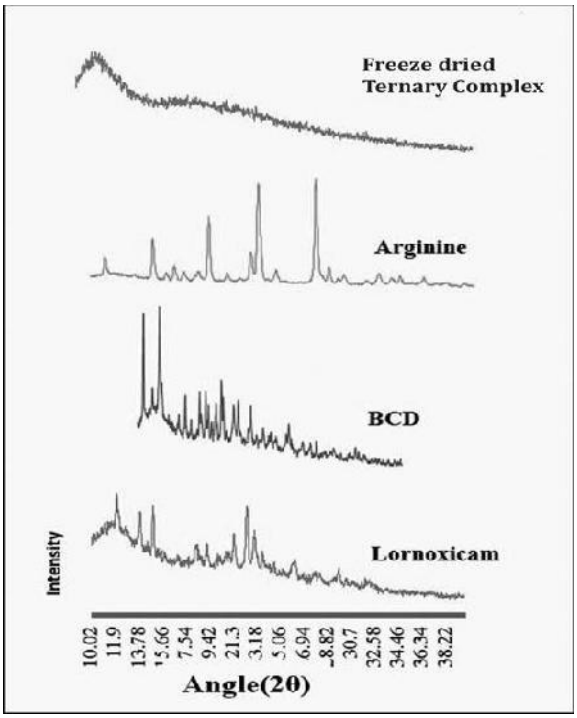

Figure 4: XRD patterns of LOR, β-CD, Arginine and LOR:β-CD:Arg Freeze dried ternary complex

Optimization of formulation

LOR has pH dependant solubility (insoluble towards lower pH i.e. in acidic pH and soluble in basic pH). Thus, by preparing freeze dried ternary complex, solubility of LOR has been significantly increased due to amorphization and micro environmental basic pH generation. The improved solubility in water as well as in pH 1.2 assist to confer the desired release of LOR which is one of the important pre-requisite for preparation of MOTS.Optimized freeze dried ternary complex was used as core in order to achieve the desired zero order drug release of various designed batches and formulation was optimized as mentioned in (Table 1) of the MOTS of LOR.

Table No.1: Different batches showing formulation variables of ternary complex of LOR loaded MOTS

Batch No.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
LOR:β-CD:Arg freeze dried complex	40.42	40.42	40.42	40.42	40.42	40.42	40.42	40.42	40.42	40.42	40.42	40.42	40.42	40.42	40.42
PEO WSR N80	105				35	35	35	35	35	35	35	35	35	35	35
PEO WSR 705		105													
PEO WSR 205			105												
PEO WSR 1105				105	70	105	140	105	105	105	105	105	105	105	105
Lactose	80.33	80.33	80.33	80.33	80.33	45.33	10.33	45.33	45.33	45.33	45.33	80.33	10.33	80.33	80.33
PVP-K30	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
	Extra granular														
Sodium Chloride	105	105	105	105	105	105	105	105	105	105	105	70	140	105	105
Aerosil 200	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Calcium stearate	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Coating weight gain of CA (%)	7	7	7	7	7	7	7	7	7	5	9	7	7	7	7
PEG 400 (%)*	20	20	20	20	20	20	20	10	30	20	20	20	20	20	20
Aperture size (mm)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.8	1

(* weight of the plasticizer with respect to weight of coating polymer)

Table No.1: Drug release kinetics of optimized batch (F6) with different R^2 values

Sr. No	Kinetic model	Parameter	value
1	zero order	R^2	0.9841
		K_0	5.06
2	first order	R^2	0.962
		K_1	0.105
3	Higuchi	R^2	0.9144
		K_H	19.873
4	Peppas	R^2	0.9588
		kKP	11.987
5	Hixon	R^2	0.8809
		kHC	0.03
6	zero order with T lag	R^2	0.9152
		k0/T lag	4.416/-2.226
7	Zero with F0	R^2	0.9152
		k0/F0	4.416/9.826

Effect of different molecular weight PEO and their combination

Polyethylene oxide (PEO) is used as suspending agent and is one of the critical parameters in modulation of lag time from MOTS. Different molecular weight of PEO with varying viscosities was tried to achieve the desired zero order release LOR from MOTS. Initially PEO WSR N80 (mol.wt. 200000), PEO WSR 750 (mol.wt. 300000), PEO WSR 205 (mol.wt. 600000) and PEO WSR 1105 (mol.wt 90000) at 30 % w/w concentration was used as shown in table 1 with batch F1, F2, F3 and F4 respectively. Figure 5 shows that with increase in

molecular weight of the PEO in core tablet there was considerable retardation of drug release from the core as evidenced by increasing lag time. This is because after entering water into the system, it hydrates the core of tablet to form a gel layer of PEO which is uniformly incorporated throughout the tablet. The rate of diffusion out of the gel layer through aperture control the overall dissolution rate and delivery of the active substance.[19]A lower molecular weight polymer will release faster than a high molecular weight grade because of low viscosity and swelling capacity of PEO and could not last for 24 hr. More than 90% drug release was observed with lower molecular weight PEO while PEO 205 and PEO 1105 having comparatively higher molecular weight gave drug release up to 24 hr but confer undesirable high lag time. Thus, in order to achieve the desired release combination of low molecular weight PEO like WSR N80 and high molecular weight PEO like WSR 1105 were used in varying ratios to form optimum viscosity suspension inside the core which reduces the lag time as shown in table 1 (batch F5, F6, F7) and Figure 5. The drug release from the batches with high molecular weight PEO is governed by the swelling of the polymer rather than by the erosion of the polymer, leading to anomalous release kinetics. However, the drug release from the low molecular weight PEO is controlled primarily by the swelling/erosion of the polymer, resulting in front synchronization and a constant release rate in presence of osmotic pressure exerted by osmotic agent.[23] Therefore, PEO WSR N80 (10% w/w) and PEO WSR 1105 (30%w/w) were found to be optimum in order to achieve the desired drug release of LOR from MOTS as shown in Figure 6.

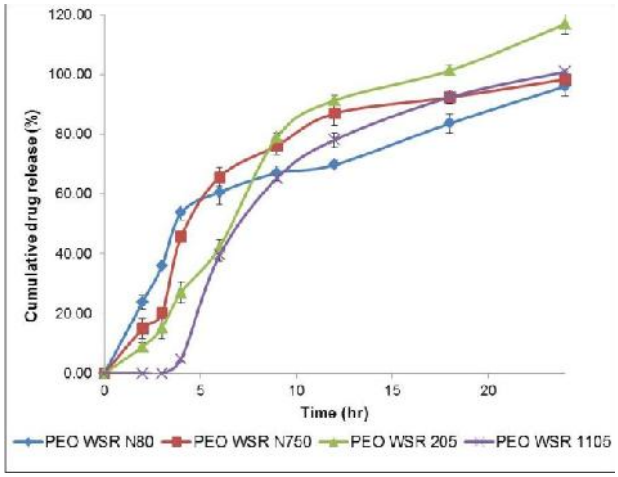

Figure 5: Effect of different mol.wt. of PEO at 30 % w/w concentration

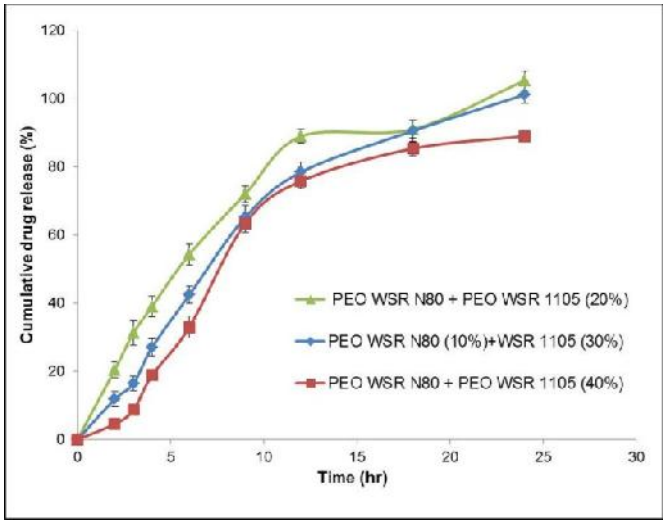

Figure 6: Effect of different combination of PEO N80 and PEO WSR 1105 at various concentrations

Effect of level of pore former on drug release

The peculiar influence of pore former on the drug release profile was studied by changing the concentration of PEG-400 in the coating layer from 10% w/w to the 30% w/w (weight of pore former with respect to coating polymer) as shown in Table 1 (batch F6, F8, F9). As depicted from Figure 7, the increment in PEG-400 level led to an increase in drug release. Since PEG-400 was a hydrophilic plasticizer, it could be leached out easily and left behind porous structure. The more PEG-400 incorporated into EC semipermeable membrane, the higher membrane permeability and faster drug release rate was obtained. With higher pore former (30% w/w), fast drug release was observed (more than 85% in 12 h). This may be due to rapid channels formation. After evaluation of drug release kinetics, F6 with pore former at 20 % w/w concentration was found optimized which follows desired first order kinetics with good R^2 values 0.9841 (Table 2). This may be because of sufficient pore formation in the release retardant layer causes desire drug release by concentration independent mechanism, whereas at 10% and 30 % concentration level, drug released by F8 and F9 found to be concentration dependent manner.[3]

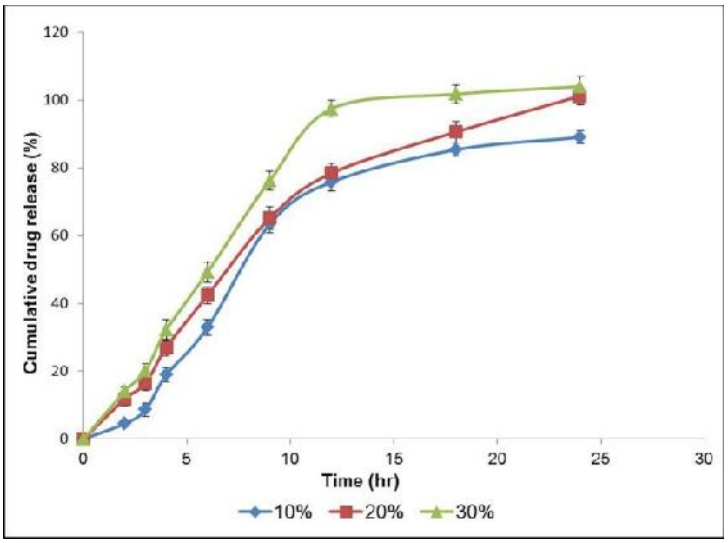

Figure7: Effect of level of pore former Peg-400 on drug release

Effect of level of release retardant and osmotic agent

After optimizing the level of pore former, effect of concentration of retardant coating polymer i.e. cellulose acetate coatingwas studied. It was observed that at lower levels of coating weight gain, 5.0% drug was released (Figure 8) very rapidly because of coating layer do not remain intact and it ruptures from around the aperture and fails to maintain total integrity of film. The erosion of coating layer is because of high hydrostatic pressure created by the presence of osmotic agent (NaCl) (Figure 9) inside the core of tablet. However, with increment in level of coating at 9%; retardation in the drug release was observed which gives undesirable high lag time. Optimized 7 % coating with 30 % NaCl as osmotic agent able to withstand the hydrostatic pressure and coating layer does not get rupture and able to maintain the perfect integrity of coating film; consequently release the drug in more controlled manner depending on osmotic pressure inside the core of MOTS. Therefore, kinetics of drug release showed that batches with level of coating 7% with 30 % osmotic agent (F 6) follow zero-order kinetics with (R^2> 0.9841), whereas batches with lower level and little higher level of coating (F 10 and F 11) showed concentration independent drug release pattern. Batch F 6 which has 7% coating with 30 % NaCl has demonstrated zero order and complete drug release over period of 24h.

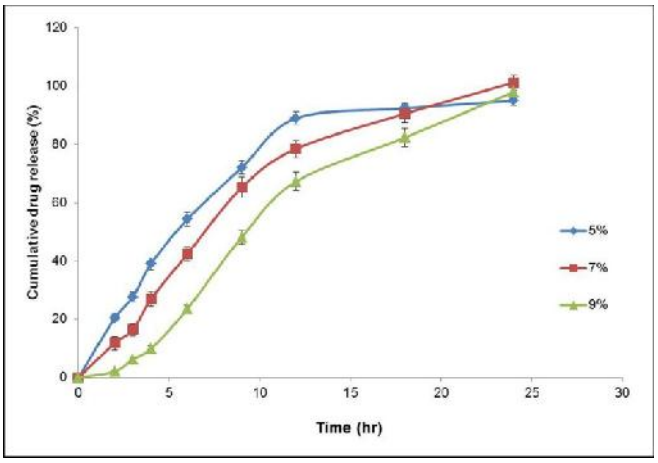

Figure 8: Effect of level of release retardant semipermeable membrane i.e. cellulose acetate coating

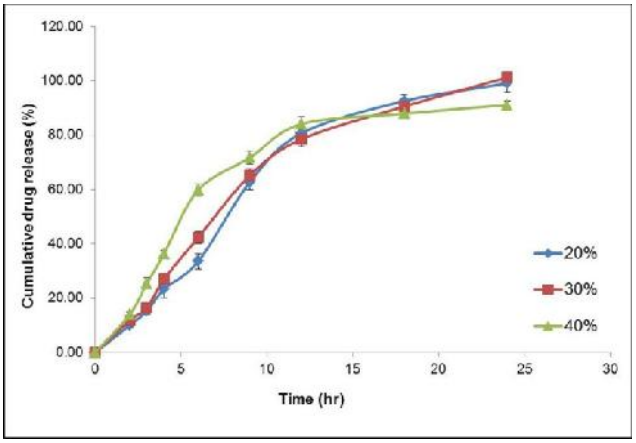

Figure 9: Effect of sodium chloride (NaCl) as an osmotic agent

Effect of hydrodynamic force on release profile

Drug release from osmotic pumps is generally not affected by change in agitational intensity i.e. speed of the paddle in dissolution apparatus.[24, 25]Figure10 shows that the release profile of LOR from the optimized formulation was almost independent of the agitational intensity of the release media. These results assure that the release from the developed formulations will be independent of the hydrodynamic conditions of the body.[3]This confirms that the coating membrane and swelling polymer plays the rate-controlling step in the mechanism of LOR release from MOTS, which is consistent with the findings from other controlled osmotic devices.[26]

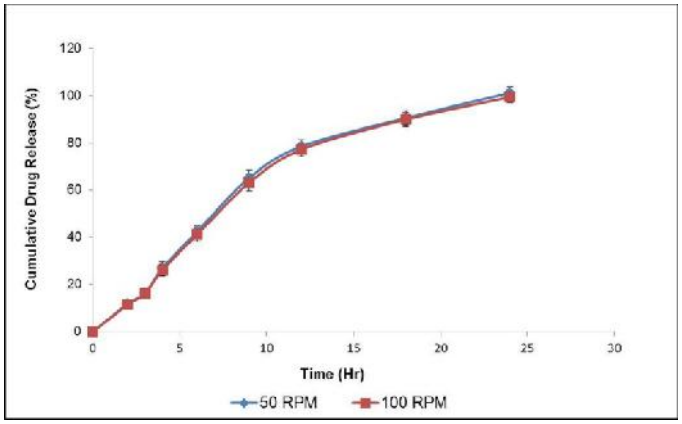

Figure10: Effect of hydrodynamic force on release profile

Effect of medium pH on drug release profile from LOR MOTS

When in vitro release studies were conducted in buffers with different pH and in distilled water, no significant difference in the release profiles was seen compared with that in phosphate buffer (pH 6.8) Figure 11 which confirmed that formulation exhibited media independent drug release. This is owing to tremendous increase in solubility of LOR in all pH conditions because of highly amorphous freeze dried ternary complex of LOR: β-CD: Arg employed in core of the MOTS of LOR Figure 2. Therefore, it can be assumed that the release properties during gastric transit will not change because of interindividual and intraindividual changes of gastric pH.

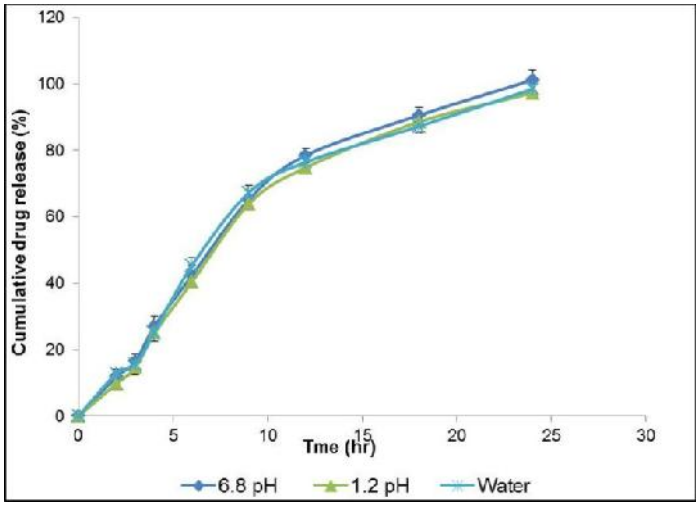

Figure 11: Drug release profiles at different pH conditions

Influence of orifice size on drug release profile

Once the tablet formulation and membrane variables were chosen, the orifice size will be the key factor to drug release. As shown in Figure12 Significant difference existed in the release profiles for orifice diameters ranging from 0.6 mm, 0.8 mm and 1 mm. However, the release rate was somewhat rapid with an orifice diameter of 1mm.This may be due to the result of diffusion from the bigger orifice. On the other hand, a zero order release was exhibited at an orifice diameter of 0.6 mm.[10]

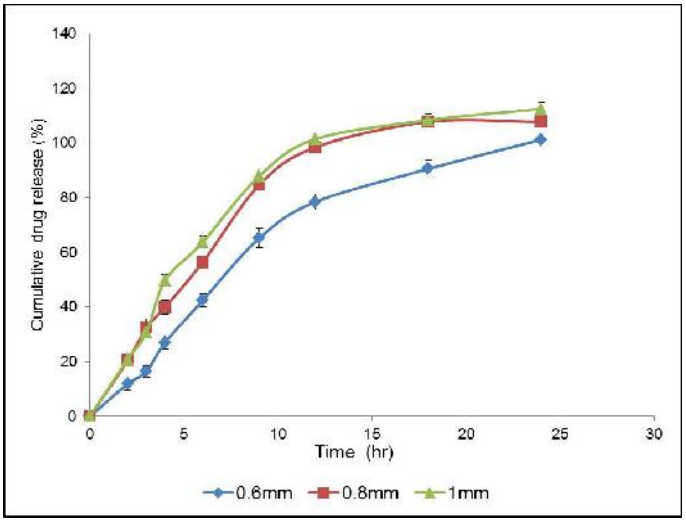

Figure 12: Influence of orifice size on drug release profile

Evaluation of optimal MOTS

Based on the study of influence of different formulation variables, the final optimized formulation of MOTS (F6) is shown in Table 1. To investigate the influence of dissolution media on drug release, dissolution of the optimal formulation were conducted in pH 1.2, water and phosphate buffer pH 6.8. Figure 9 showed the release profiles of the MOTS in the above mentioned release media. In above all the dissolution medium drug release was not significantly different. Therefore, it may be expected that the drug release from this MOTS will be independent on the gastrointestinal fluid. To study the effect of stirring rate on the drug release profiles, dissolution of the optimal MOTS were carried out at varying stirring rates of 50 and100 rpm. Figure 8 shows that an increase in the rate of stirring did not significantly affect the release rate of drug. Thus, the mobility of the gastrointestinal tract may barely affect the drug release of the MOTS. The MOTS was simple to prepare since it is unnecessary for a push compartment and to consider which side should be drilled. The optimal MOTS was found to delivered LOR at a rate of approximately zero order up to 24 h in pH 6.8, water and in pH 1.2. Cumulative release at 24 h is almost 100% and the drug release rate adjusted by changing the amount of combination of different molecular weight PEO in core of the tablet, the percentage of PEG-400 in membrane and percentage of coating weight gain. Furthermore, this freeze dried amorphous ternary core MOTS is independent on environment media and stirring rate. In conclusion, MOTS designed in this study is a good controlled delivery system for water-insoluble and the drug having pH dependent solubility.

Mechanism of drug release from MOTS

Drug releasing from MOTS is somewhat different from that of EOP. In operation, the PEO osmotic core imbibes water from the surrounding medium via the semipermeable membrane. Subsequently, the PEO swells and dissolves. Due to the viscosity of PEO solution, the LOR:β-CD:ARG amorphous freeze dried ternary complex suspension is formed inside the core of tablet. Then due to the expansion of PEO and osmotic pressure exerted by osmotic agent between the membranes, the suspension is delivered out of the device via the orifice, as shown schematically in Figure 10.

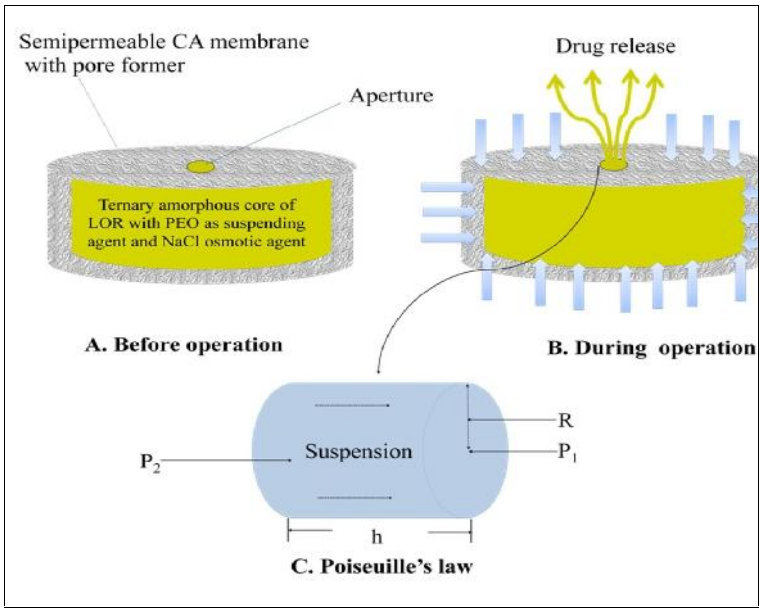

Figure 13: Schematic representation showing mechanism of MOTS

Poiseuille's law of laminar flow can be applied to this system. The Poiseuille's law can be expressed as-

$$\frac{dv}{dt} = \frac{\pi}{8}\frac{R^4}{\eta} = \frac{P_1 - P_2}{L} \quad (2)$$

Where dV/dt is the flow rate in the tube, R the radius of tube, g the viscosity of flow, P_1 - P_2 is the pressure difference between two end of tube and L the length of the tube. However, when Eq. (1) is applied to MOTS, the concentration of drug in suspension must be also considered. Then, under a certain fluid permeability of membrane, Eq. (1) has been modified to Eq. (2)

$$\frac{dM}{dt} = \frac{\pi C}{8} \frac{R^4}{\eta} = \frac{P_1 - P_2}{h} \quad (3)$$

Where dM/dt is the drug release rate, C is the concentration of drug in suspension, R the radius of orifice, g the viscosity of suspension, P_1-P_2 the pressure difference between membrane, h the thickness of membrane. From Eq. (2), the drug release rate is directly proportional to C, R^4 and (P_1 - P_2), and inversely proportional to g and h. Compared toEOP, drug release rate of MOTS is independent on the drug solubility provided that drug should be in solubilised state in core of the tablet. In order to keep the constant drug release rate, the percent of drug in suspension (C) must be kept constant; sufficient PEO concentration is required to counteract the precipitation of drug. The suspension viscosity (η) is very important in the MOTS; if η is too high, the release rate will be decreased; if η is too low, drug powder will easily precipitate. In addition, the pressure difference between two sides of the membrane (P_1-P_2) is important also, which includes osmotic pressure of PEO solution and the swelling force of PEO. If the polymer swells too much, the membrane will be broken and coating of CA film will loss it integrity; if the polymer has a low expanding property, the drug release rate will be decreased. PEO is such a polymer that has a suitable viscosity and expanding property, so it functions well in the MOTS. Eq. (2) can also be used to explain the influence of orifice size and membrane thickness on the drug release in MOTS. However, much more complete experiments, including measuring the pressure difference between membrane (P_1-P_2) which includes osmotic pressure of PEO solution and the swelling force of PEO, are needed to proceed so that the data can be used to fit Poiseuille's equation and obtain some parameters. In summary, drug release from MOTS can be contributed to the osmotic, suspending and expanding property of PEO.[27]

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Conclusions

The monolithic osmotic tablet system (MOTS) using freeze dried amorphous ternary complex as core was used to increase the solubility of LOR and making it pH independent. Combination of different molecular weight of PEO perfectly works because of formation of optimum viscosity of suspension to achieve the desired zero order release without lag time. The optimal MOTS were found to deliver LOR at a rate of approximately zero order up to 24 h in pH 6.8, 4.5 and pH1.2. Cumulative release at 24 h is independent on environment media and stirring rate. From the drug release mechanism of the MOTS, the application of MOTS designed in the current study is independent on the drug solubility. Therefore, MOTS restrain ternary freeze dried amorphous core can be used in the field of oral controlled release delivery of different drugs, especially for water-insoluble and those having pH dependant solubility.

Authors Statement

The authors declare no conflict of interest.

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