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PREPARATION AND EVALUATION OF OSMOTIC PUMP SYSTEMS OF SOFT GELATIN CAPSULES, L-OROS SOFTCAP, OF IBUPROFEN

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ABSTRACT

Controlled drug delivery systems offer spatial control over the drug release. Osmotic pumps are most promising systems for controlled drug delivery. The objective of this study was development of L-OROS SOFTCAP delivery system as a controlled release system and to investigate the influence of different factors. L-OROS® SOFTCAP™ was prepared by coating a gelatin capsule with an inner barrier layer using cellulose acetate and thiethyl citrate, an expandable osmotic layer which was designed by HPMC and NaCl and a rate controlling membrane. After coating, the system was drilled mechanically. The effect of type and ratio of various polymers, weight of osmotic compartment, weight of semipermeable membrane and barrier membrane on drug release profile was investigated and the best formulation of each step was selected. Studies showed that amount of usage osmotic agent and ratio of that amount to semipermeable membrane weight and thickness were effective factors on drug release profile. The release of soft gels was extended from 1 to 10 hours with designing osmotic pumps on the surface of them.

KEYWORDS : *Osmotic pumps, barrier layer, drug delivery, controlled release, semipermeable layer, kinetc.*

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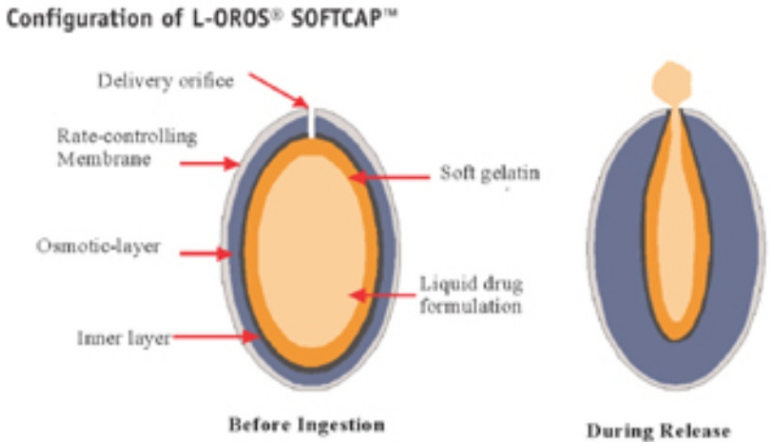
INTRODUCTION

Oral rout has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constrains and flexible design of dosage forms. Many conventional drug delivery systems have been designed by various researchers to modulate the release a drug over an extended period of time and release. [1,2] The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physicochemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH of the gastro-intestinal and etc. [2,3] However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract. Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. [2] Osmotic systems for controlled drug-delivery applications are well established, both in human pharmaceuticals and in veterinary medicine. Several one compartment and two-compartment osmotic systems have been reviewed previously.[4,5] The historical development of osmotic systems includes seminal contributions such as the Rose–Nelson pump, the Higuchi–Leeper pumps, the AlzetR and OsmetR systems, the elementary osmotic pump, and the push-pull or GITSR system. [4] Osmotic drug-delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane coating. This coating has one or more delivery ports through which a solution or suspension of the drug is released over time. The core consists of a drug formulation that contains an osmotic agent and a water swellable polymer. The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating.[4,6-7] Osmotic drug delivery systems for oral and parenterals use offer distinct and practical advantages over other means of delivery. The following advantages have contributed to the popularity of osmotic drug delivery systems:

1. Easy to formulate and simple in operation.
2. Improve patient compliance with reduced frequency.
3. Prolonged therapeutic effect with uniform blood concentration.
4. They typically give a zero order release profile after an initial lag.
5. Deliveries may be delayed or pulsed if desired.
6. Drug release is independent of gastric pH and hydrodynamic condition.
7. They are well characterized and understood.
8. The release mechanisms are not dependent on drug.
9. A high degree of in-vitro and in-vivo correlation (IVIVC) is obtained in osmotic systems.
10. The rationale for this approach is that the presence of water in git is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.
11. Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
12. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
13. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters. [4-10]

Figure1. Schematic structure of LOROS® SOFTCAP™ systems.



Key parameters which influence the design of osmotic controlled drug delivery system include: Orifice size, solubility, osmotic pressure, semipermeable membrane. Basic component of osmotic systems are: drug, semipermeable membrane, osmotic agent, flux regulator, wicking agent, pore forming agent, coating solvent, plasticizer. [4] Figure 1 shows a schematic structure of oral osmotic drug delivery systems based on soft gelatin capsules. Based on their design and the state of active ingredient, osmotic delivery systems can be Classified as follows: 1- Osmotic Delivery Systems for Solids: Type I**:** Single compartment. In this design, the drug and the osmotic agent are located in the same compartment and are surrounded by the semipermeable membrane (SPM). Both the core components are dissolved by water. Type II: Multiple compartments. In this design, drug is separated from the osmotic compartment by an optional flexible film, which is displaced by the increased pressure in the surrounding osmotic compartment, which, in turn, displaces the drug solution or suspension. 2- Osmotic Delivery Systems for Liquids. Active ingredients in liquid form are difficult to deliver from controlled release platforms because they tend to leak in their native form. [2] Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. They are of three types: a) L OROS hard cap b) L OROS soft cap c) delayed liquid bolus delivery system. (8) Soft gelatin capsules contain oily drug solutions or suspension of drug which rounded with a layer containing gelatin, plasticizer, water, color and antioxidants. Some benefits of soft gelatin capsules are rapid drug release and increasing of bioavailability, easier swallow, more beautiful shape, longer shelf life and simpler formulation rather than tablets.[11,12] In L-OROS soft capsule system, the liquid drug is encased in a soft gelatin capsule surrounded by a barrier layer, an osmotic engine, and a semi-permeable membrane. The barrier layer separates the soft gelatin capsule from the osmotic engine, minimizing hydration of the soft capsule to prevent its mixing with the drug layer. The delivery orifice in L-OROS system is drilled through the semi-permeable membrane, osmotic engine, and barrier layer. When the osmotic engine expands, it compresses the soft gelatin capsule, pushing the drug formulation out through the delivery orifice. [13] Some ODDS (Osmotic Drug Delivery Systems) formulation available in market are listed below: Prazocin, Pseduephedrine, Isradipine, Verapamil, Glipizide and etc. [14] Selected drug in this study was Ibuprofen. Ibuprofen is a well-known hydrophobic oral non-steroidal anti inflammatory drug (NSAID) (Wilson et al. 1989) and is the first phenylalkanoic acid approved by the FDA for general analgesic use. Similar to other drugs of this group, it has a wide spectrum of gastrointestinal side effects ranging from mild dyspepsia to gastric bleeding. The gastric irritation is mainly due to the free carboxylic acid group in the chemical formula. Due to its short plasma half-life of 1–3 h following

oral dosing and the gastric irritation, ibuprofen is an ideal candidate for preparing prolonged or controlled release drug products. [15] In this study design of oral osmotic pump system of gelatin capsules for controlled drug rerelease and improved bioavailability was investigated. Osmotic pump system of soft gelatin capsules was designed based on Advil Liquid-Gels. For forming of barrier layer cellulose acetate was used and effect of weight of this layer on drug release profile was studied. For designing of osmotic part, HPMC (4000 and 6 cps mixture) and NaCl were used as hydrophil polymers and Inorganic water-soluble osmotic agent respectively and effect of ratio of HPMC 4000 to 6 cps and usage weight of NaCl on drug release profile was investigated. Effect of weight of semipermeable membrane on drug release was studied too.

MATERIAL AND METHODS:

Materials:

Cellulose acetate (BDH Chemicals, British), Hydroxy Propyl Methyl Cellulose, HPMC 4000 an 6 cps, (Merck, Germany), Ibuprofen (Temad, Iran), Three Ethyl Cytrate, Acetone, Potassium Dihydrogene Phosphate and NaCl were purchased from Merck, Germany.

Methods:

Osmotic pump systems of soft gelatin capsules contains: barrier membrane, osmotic compartment, semipermeable membrane and small orifice on encapsulated gelatin capsules.

Barrier membrane:

For create of barrier membrane on the surface of soft gelatin capsules of ibuprofen, cellulose acetate was used in concentration of 4% (w/v) in acetone-ethanol mixture (50-50) and three ethyl citrate as a plasticizer was added to the mixture equal to 25% weight of cellulose acetate. The above solution was sprayed on the surface of the surface of soft gelatin capsules in different designed weight include: 15, 20, 25 and 30 mg and effect of this difference on drug release was investigated. Desired formulation based on weight of barrier membranes were named a_1, a_2, a_3 and a_4 respectively. For selection of suitable plasticizer in this stage, primary studies were done with different plasticizers including: Di Butyl Phthalate (DBP), Three Ethyl Citrate, Three Ethyl Citrate and Poly Ethylene Glycol (PEG) mixture and Three Ethyl Citrate and Cellulose acetate mixture was selected.

Osmotic compartment:

Design of osmotic compartment was done using HPMC (4000 and 6 cps mixture) and NaCl. In first step, amount of NaCl was fixed and effect of ratio of HPMC 4000 to 6 cps was studied to find the best ratio. Table 1 shows desired ratios. To create different osmotic compartments based on table 1. Mixture of HPMC was dissolved in 150 ml ethanol 70° at 75 rpm for 1 hour. Then NaCl which was dissolved in 30 ml distilled water, was added to HPMC mixture and mixing was continued for more 30 minutes. 200 mg of each formulation (A-F) was sprayed on the surface of capsules. For evaluation of effect of this compartment weight on release profile, different amounts include 150, 200 and 250 mg of formulation A was sprayed on surface of capsules and they were coded as b_1, b_2 and b_3 respectively. At another step on the surface of formulation a_2, all components which were presented in table 2 were sprayed on capsules a_2 to reach 200 mg of weight. The designed formulations were shown in table 3. In next step effect of NaCl amount was studied regarding table 2.

Table 1. Different ratio of HPMC 4000 to 6 cps in osmotic compartment

Formulation Nomination	Weight (g)		Ratio		NaCl (g)
	HPMC 6 cps	HPMC 4000cps	HPMC 6 cps	HPMC 4000cps	
A	6	1	6	1	7
B	6	1.2	5	1	7
C	6	1.5	4	1	7
D	6	2	3	1	7
E	6	3	2	1	7
F	6	6	1	1	7

Table 2. Different amount of NaCl in osmotic compartment

Formulation Nomination	NaCl (g)	Wight (g)	
		HPMC 6cps	HPMC 4000cps
G	1	6	1
H	3	6	1
I	5	6	1
A	7	6	1
J	9	6	1

Table 3. Different designed formulations using formulation a_2

Formulation Nomination	Weight of barrier membrane (mg)	Code of osmotic component	Weight of osmotic compartment
a_2Gb_2	20	G	200
a_2Hb_2	20	H	200
a_2Ib_2	20	I	200
a_2Ab_2	20	A	200
a_2Jb_2	20	J	200

Semipermeable membrane:

In this stage cellulose acetate 4% was used. Different formulations based on different weight of semipermeable membrane were created as are shown in table 4-6.

Table 4. Different formulations which made from a_2Ab_1 with different semipermeable membrane weight

Formulation Nomination	Weight of semipermeable membrane(mg)
$a_2Ab_1c_1$	15
$a_2Ab_1c_2$	20
$a_2Ab_1c_3$	25
$a_2Ab_1c_4$	30

Table 5. Different formulations which made from a_2Ab_2 with different semipermeable membrane weight

Formulation Nomination	Weight of semipermeable membrane(mg)
$a_2Ab_2c_1$	15
$a_2Ab_2c_2$	20
$a_2Ab_2c_3$	25
$a_2Ab_2c_4$	30
$a_2Ab_2c_5$	40
$a_2Ab_2c_6$	50

Table 6. Different formulations which made from a_2Ab_3 with different semipermeable membrane weight

Formulation Nomination	Weight of semipermeable membrane(mg)
$a_2Ab_3c_1$	15
$a_2Ab_3c_2$	20
$a_2Ab_3c_3$	25
$a_2Ab_3c_4$	30

Orifice making:

At the end with a mechanical force using drill with 1mm diameter, orifice was designed in condition which 3 layers of osmotic pump were holed but the core, soft gelatin capsule, was without any scare.

Release study:

Drug release profile of Advil liquid capsules was studied using phosphate buffer solution(PBS), pH: 7.2 and according the USP method using UV Spectrophotometer system (Shimadzu, Japan) which was set at λ_{max}: 220 nm. The dissolution test condition was as described below:

Paddle system was used, medium volume was 1000 ml PBS pH 7.2, temperature was set on 37±0.5° C and paddle rotation rate was 100 rpm and sample size was 5ml with refresh PBS replacement. For evaluation of effect of barrier membrane weight on drug release profile, formulation A was sprayed on the surface of formulation a_1-a_4 to receive 150 mg of weight. After adding 20 mg semipermeable membrane and making 1 mm diameter orifice, dissolution test was done on these samples too on the above condition. Studied formulations were listed in table 7. For investigation of effect of ratio of HPMC 4000 TO 6 cps, formulations as listed in table 8 were designed. For study of osmotic compartment weight effect on drug release profile three formulation as are shown in table 9 were designed. Table 10 shows formulation that were created for evaluation of effect of NaCl amount on drug release profile.

Table 7. Studied formulations for effect of barrier membrane weight on drug release profile

Formulation Nomination	Barrier membrane weight (mg)	Osmotic compartment weight (mg)	Semipermeable membrane weight (mg)
a_1Ab_1c2	15	150	20
$a_2Ab_1c_2$	20	150	20
$a_3Ab_1c_2$	25	150	20
$a_4Ab_1c_2$	30	150	20

Table 8. Different formulations which were designed for investigation of effect of HPMC 4000 to 6 cps on drug release profile

Formulation Nomination	Barrier membrane weight (mg)	Osmotic compartment formulation code	Osmotic compartment weight (mg)	Semipermeable membrane weight (mg)
$a_2Ab_2c_2$	20	A	200	20
$a_2Bb_2c_2$	20	B	200	20
$a_2Cb_2c_2$	20	C	200	20
$a_2Db_2c_2$	20	D	200	20
$a_2Eb_2c_2$	20	E	200	20
$a_2Fb_2c_2$	20	F	200	20

Table 9. formulations which were designed for evaluation of effect of osmotic compartment weight on drug release profile

Formulation Nomination	Barrier membrane weight (mg)	Osmotic compartment weight (mg), formulation A	Semipermeable membrane weight (mg)
$a_2Ab_1c_2$	20	150	20
$a_2Ab_2c_2$	20	200	20
$a_2Ab_3c_2$	20	250	20

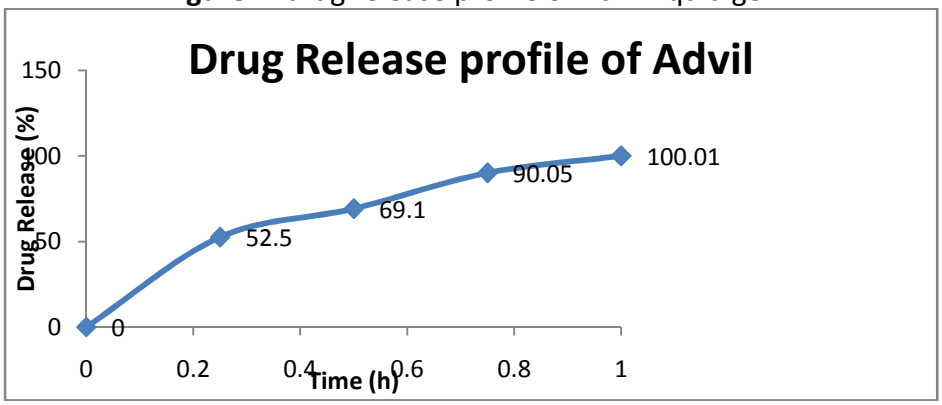
Table 10. formulations which were designed to evaluate effect of NaCl weight on drug release profile

Formulation Nomination	Barrier membrane weight (mg)	Osmotic compartment formulation code	Osmotic compartment weight (200mg)	Semipermeable membrane weight (mg)
$a_2Gb_2c_2$	20	G	200	20
$a_2H\ b_2c_2$	20	H	200	20
$a_2I\ b_2c_2$	20	I	200	20
$a_2A\ b_2c_2$	20	A	200	20
$a_2J\ b_2c_2$	20	J	200	20

RESULTS AND DISCUSSION:

Figure 2 shows drug release profile of Advil liquid gels in PBS, pH 7.2. As is clear, after one hour almost 100% of ibuprofen released through soft gelatin capsules. But after design of osmotic pump system, release of drug continued for 10 hours. In other studies release of ibuprofen sustained using other drug delivery systems, Arica et al. designed some alginate beads of ibuprofen which could sustained release of drug for 7 hours. [15]

Figure 2. drug release profile of Advil liquid gel.



Comparison of drug release profile of formulations with different barrier membrane:

Figure 3 shows drug release profile through designed osmotic pumps with different barrier membrane weights, in this stage capsules with equal HPMCs and osmotic compartment which were different in different barrier membrane weights were studied. Results show that the difference in barrier membrane weight could not influence the rate of drug release so the formulation which contains 20 mg coat of barrier membrane was selected as the best for continue of the study. Figure 4 shows drug release profile through formulations with different HPMCs ratios, because of any significant effect of HPMCs ratios, formulation A which contained less HPMC 4000cps and let researchers to spray that easier on the surface of capsules, was selected.

Figure 3. Drug release profile of different formulations with different weight of barrier membrane.

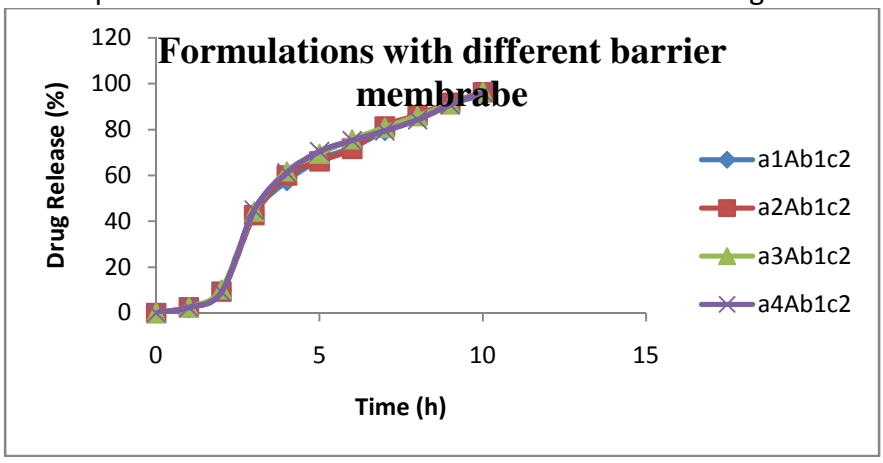


Figure 4. drug release profile of formulations with different ratio of HPMC 4000 & 6 cps.

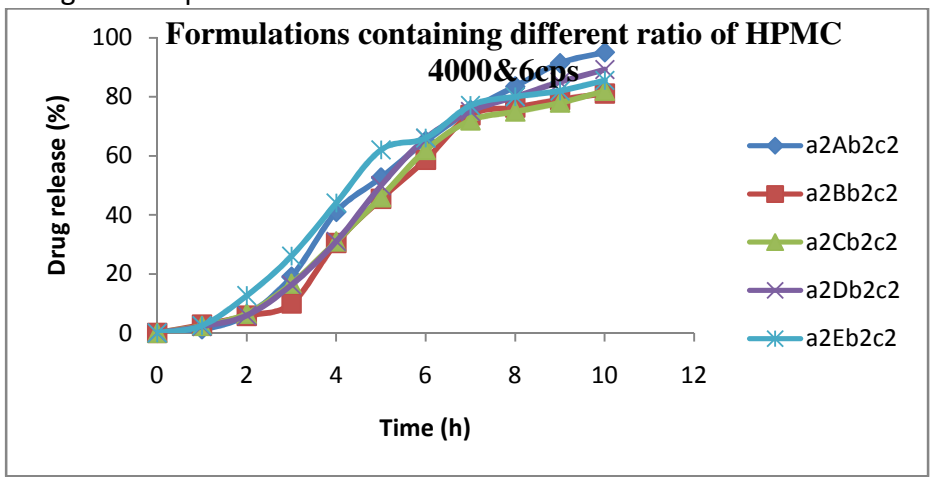
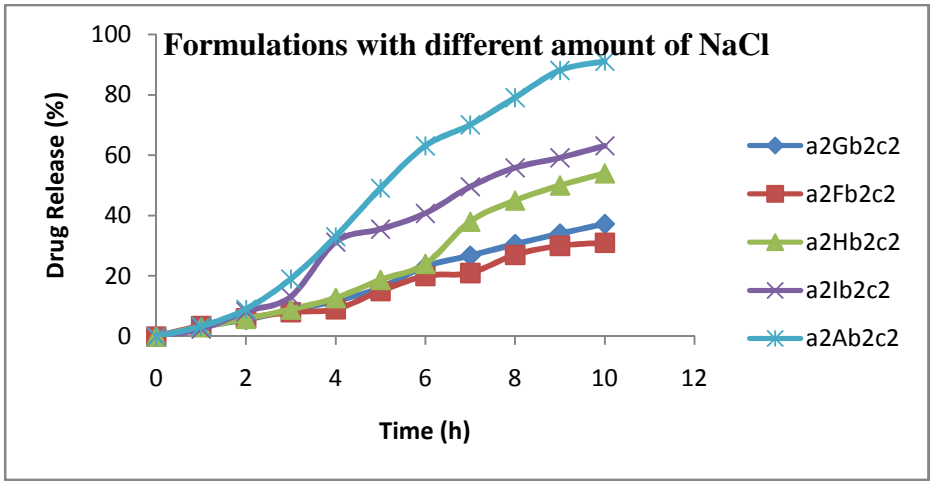


Figure 5 shows effect of NaCl amount on drug release, results show that formulations $a_2Hb_2c_2$ and $a_2Gb_2c_2$ which contain 1 and 3 mg NaCl respectively, are not suitable formulations and after dissolving of NaCl, it can't create enough osmotic pressure to help exit of drug from system, formulation $a_2Ib_2c_2$ with 5 g NaCl showed more drug release but $a_2Ab_2c_2$ with 7 g NaCl showed the best drug release profile. Formulation $a_2Jb_2c_2$ with 9 g NaCl show a rapid drug release at first but it could not show a suitable profile. So it seems in our study the best amount of NaCl is 7 g. For investigation of effect of osmotic compartment weight, formulations a_2 were designed, and three different weight of osmotic compartment was sprayed, 150, 200 and 250 mg which showed drug release as described below:

Figure 5. Drug Release profile of formulations with different amount of NaCl.



Formulation $a_2Ab_1c_2$ showed suitable drug release pattern but $a_2Ab_3c_2$ scratched after 2 hours in dissolution medium and test could not be continued. The best release profile in this stage was for $a_2Ab_2c_2$. Study of Ozdemir and Sahin showed that the release rate of ibuprofen was influenced by the concentration of osmotic agents sodium chloride and polyethylene in their designed osmotic pump of ibuprofen. [16] Shah et al observed the effect of amount of NaCl on drug release profile of push-pull osmotic drug delivery systems. [17] Kanagale et al studied on the effect of variables on drug release through osmotic pump delivery systems. [18] Some formulations of a_2 group were studied to find relation between weight of semipermeable membrane weight and drug release, studies show that increasing of that weight cause to reducing of drug release and it seems

because of less absorbance of water because of more diameter of semipermeable membrane and less osmotic pressure. Formulations $a_2Ab_2c_2$ and $a_2Ab_2c_3$ with 20 and 25 mg semipermeable membrane show the best release pattern, formulation $a_2Ab_2c_1$ scratched after 2 hours because of thin semipermeable membrane and formulations with 30, 40 and 50 mg membrane have not suitable release. Also it seems that the weight of osmotic compartment and semipermeable membrane should match with each other and these tow parameters are dependent.

Drug release kinetics study:

The optimized formulation in each step subjected to the release kinetics study. The R^2 value for Higuchi, first order and zero order release was studied. It was seen from the studies that zero order showed higher regression value than the other formulation of 0.97. Hussan Reza et al designed bilayer tablets as osmotic delivery system and the best fitted release model of their formulation was zero order too. [19]

CONCLUSION:

Osmotic pumps are the most reliable controlled drug delivery system. It uses osmotic pressure for controlled delivery of active agent. The first report of an osmotic effect dates to Abbenollet (1748) and it is predicted that future of osmotic drug delivery system will be excellent. This study shows that osmotic pump delivery system could be reliable system for design of controlled release dosage form of ibuprofen, authors would like to continue this field of study with *in-vivo* studies.

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