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FORMULATION AND EVALUATION OF CONTROLLED POROSITY OSMOTIC TABLET OF VERAPAMIL HYDROCHLORIDE

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ABSTRACT: Verapamil hydrochloride is a water-soluble drug, so it is suitable to develop controlled porosity osmotic pump. As Verapamil HCl is a short-acting drug, so developed formulation provides the advantages of controlled release formulations. The developed formulation provides advantages of less steps of manufacturing procedure, no need for laser drilling, and economical, all of which made the procedure easily amenable to mass production using conventional tablet machines. Verapamil HCl 120 mg core formulations were prepared coated with film former (cellulose acetate): pore former (sorbitol). The effect of different formulation variables, namely, membrane weight gain, and amount of pore former in the membrane, were studied. Verapamil HCl release was inversely proportional to the membrane weight (coating thickness) but directly related to the initial amount of pore former (sorbitol) in the membrane. Drug release from the developed formulations was independent of pH but dependent on the osmotic pressure of the release medium. Verapamil HCl release from the developed formulation follows zero-order. The drug release from formulation was proved as dependent on osmotic pressure only. Results of SEM studies showed the formation of pores in the membrane after coming in contact with aqueous dissolution fluid from where the drug release occurred. The manufacturing procedure was found to be reproducible, and formulations were stable after three months of accelerated stability studies.

INTRODUCTION: For many decades, conventional dosage forms, which are of prompt releasing nature, are used for the treatment of acute and chronic diseases. The conventional dosage forms provide no control over the release of the drug. Recently, several technical advancements have been made. These have resulted in the development of new techniques in drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to tissue.

It is advantageous to deliver some drugs with a short half-life and which are to be given frequently for chronic ailments in the form of controlled release formulations. The majority of existing oral controlled release systems are matrix-based, and their principle drug release mechanism is based on drug diffusion through the matrix system. The diffusion is altered by the pH of the medium, the presence of food, hydrodynamic conditions, and the body's other physiological factors, all of which can cause difficulty in controlling the drug release rate

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and result in poor *in-vivo – in-vitro* correlations (IVIVC) [1, 2].

The objective of the work is to release the drug from these osmotic systems independent of the physiological factors of the gastrointestinal tract (pH) and to get zero-order drug release.

Basic Components of Osmotic Systems:

1. Drug
2. Osmogen
3. Semipermeable membrane
4. Coating solvents
5. Pore-forming agents
6. Plasticizers

MATERIALS AND METHODS: Verapamil HCl, MCC, Magnesium Stearate, Talc, Sorbitol, Acetone, IPA, Cellulose Acetate were used in work done at Pad. Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune.

Development of Analytical Method (UV Spectrophotometry): [3] UV spectroscopic method is chosen for the analysis of Verapamil HCl. The wavelength of 278 nm was selected for further study.

Optimization of Sodium Chloride in Core Tablet: [4] Incorporating sodium chloride can modulate the release of drug within the system to control drug release. For the optimization of sodium chloride in the core tablet, preliminary formulations were prepared by incorporating sodium chloride into the core tablet in 10, 15, 20, 25, 30, 40 mg. Increments. The tablets were prepared by direct compression technique. The ingredients were weighed accurately as per the formula given in **Table 1**. The ingredients were kneaded in the mortar and pestle for 15-20 min.

TABLE 1: OPTIMIZATION OF SODIUM CHLORIDE IN CORE TABLET

Ingredients	Weight (mg)					
	D1	D2	D3	D4	D5	D6
Verapamil hydrochloride	120	120	120	120	120	120
Sodium chloride	10	15	20	25	30	40
Lactose	20	20	20	20	20	20
MCC	143	138	133	128	123	118
Mg stearate	5	5	5	5	5	5
Talc	2	2	2	2	2	2
Total Weight	300	300	300	300	300	300

The core tablets were compressed at an average weight of 300 mg using 10 mm concave punches and 6-7 kg/cm^2 hardness in 8 stations rotary tablet machine.

Coating Process:

Preparation of Coating Solution: [4, 5] The coating solution containing cellulose acetate, sorbitol (pore former), and PEG 400 (plasticizer) was prepared as per the formula given in **Table 2**. Accurately weighed quantity of cellulose acetate was added to acetone (70% w/w). The mixture was stirred until the formation of a clear solution. The accurately weighed quantity of sorbitol (25% w/w of the total weight of polymer) was firstly dissolved in a small quantity of deionized water and then mixed with IPA (30% w/w). The weighed quantity of PEG (5% w/w of the total weight of polymer) was added to the IPA (30% w/w) solution. The solution was then added slowly to the cellulose acetate solution. The mixture was stirred continuously for 30 min.

TABLE 2: FORMULATION OF COATING SOLUTION

Ingredients	Concentration (%w/w)
Cellulose acetate	4
Sorbitol	25 (of total wt. of polymer)
PEG 400	5
Acetone : IPA	70 : 30

Dip Coating: [5] Tablets were coated by the dip-coating process. 4% cellulose acetate solution was used for coating. The coating solution was prepared as per the formula given in **Table 2**. The coating of the core tablet was done manually by holding each tablet with the help of forceps. The coated tablets were dried by keeping them at room temperature for 24 h. Weight gain maintained at 4% w/w. The thickness of the coated tablets measured by using a digital Vernier caliper. The tablets were evaluated by studying the release study for 6 h, in a 900 ml dissolution medium using USP Apparatus 2 (Paddle) with 50 rpm.

Evaluation of Consistency of Coat: To study the consistency of coat, formulations were formulated using NaCl (30 mg) as an osmogen (excess of osmogen burst external coat). The tablet comprised of Verapamil hydrochloride (120 mg), sodium chloride (30 mg), lactose (20 mg), MCC (123 mg), magnesium stearate (5 mg) and talc (2 mg).

The tablets were then coated with a coating composition, which was constant for the

formulations **Table 2** to get a weight gain of 3, 4, 5, 6, 7, and 8% w/w **Table 3**. The tablets were evaluated by studying the consistency of coat for 8hr, in 900 ml dissolution medium using USP Apparatus 2 (Paddle) with 50 rpm. The consistency of the coat at various % weight gains was summarized in **Table 3**.

TABLE 3: PRELIMINARY FORMULATIONS FOR EVALUATION OF CONSISTENCY OF COAT

Formulation Code	% Weight Gain
D1	3
D2	4
D3	5
D4	6
D5	7
D6	8

Evaluation of Osmotic Coated Tablets: [6, 7] Prior to the compression tablets, blends were evaluated for their bulk density and tapped density, and from these values, the % compressibility and Hausner's ratio were calculated [6]. After compression, the tablets were evaluated for their hardness, thickness, and weight variation.

***In-vitro* Dissolution Test:** [8] Dissolution test for drug release study of formulations labeled extended-release of Verapamil HCl is carried out by Medium: Buffer of pH 7.5, 900 ml.

Apparatus II: 50rpm

The Optimized Formulation was then Further Evaluated for Effect of Various Concentrations of Pore Forming Agent sorbitol: [9] In order to study the effect of various concentration of pore former on *in-vitro* drug release, the tablets were coated with pore former 15% w/w, 20% w/w, 25% w/w and the without pore former, the % weight gain of tablets were kept constant. The weight gain by the tablets was 5 ± 0.5%. Formulations were done as per the formula given in **Table 4**.

TABLE 4: FORMULATIONS FOR EVALUATION OF EFFECT OF PORE FORMER

Ingredients	Weight (mg)			
	F1	F2	F3	F4
Verapamil HCl	120	120	120	120
MCC	123	123	123	123
NaCl	30	30	30	30
Lactose	20	20	20	20
Mg. stearate	5	5	5	5
Talc	2	2	2	2
Sorbitol (% w/w)	15	20	25	-

Kinetics of Drug Release: [10, 11, 20] The dissolution profile of all the formulations were fitted to zero-order kinetics, first-order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model.

Effect of pH on Drug Release: [12, 13] *In-vitro* dissolution studies were performed using USP Apparatus 2 (Paddle) in different release media (phosphate buffer pH 4, 6.8) maintained at 37 °C ± 0.5 °C and 50 rpm. The optimized formulation (F3) was selected for the study of the effect of pH on drug release. The responses were noted in triplicate.

Surface Morphology Study: [14] To evaluate the surface morphology of the coating membrane, surfaces of the optimized formulation (F3) were examined using scanning electron microscopy both before and after dissolution (XL30 ESEM TMP+EDAX, Philips). Membranes were dried at 45 ºC for 12 h and stored between in a desiccator until examination.

Stability Study: [15, 16] The optimized formulation (F3), which gave desired zero-order release for an extended period of time was selected, packed in aluminum foil and subjected to stability studies as per ICH guidelines, 40 ± 2 °C and 75 ± 5% RH (Thermolab). Samples were withdrawn at time intervals of 1, 2, and 3 months. The samples were evaluated for appearance, assay and *in-vitro* release profile.

Comparative Study of CPOP and EOP: [17] The formulation for EOP comprised of Verapamil hydrochloride (120 mg), sodium chloride (30 mg), lactose (20 mg), MCC (123 mg), magnesium stearate (5 mg) and Talc (2 mg) and coated with5% weight gain (optimized level of factorial formulation was considered) without pore former (sorbitol). The new formulated tablets were drilled with mechanical drill. Orifice size 0.5 mm (F8), 0.8 mm (F9) and 1 mm (F10) were selected.

Comparative Study of CPOP and Marketed Sustained Release Tablet: [21] The comparative study was carried out between marketed formulation

i.e. Calaptin 120 SR tablet and CPOP by carrying out a dissolution study of the marketed formulation.

RESULTS AND DISCUSSION:

Evaluation of Osmotic Tablets:

Optimization of Sodium Chloride in Core Tablet: A preliminary trial with 10 mg sodium chloride into the core tablet revealed a slow drug release rate at from the system. The results revealed that incorporating sodium chloride at a concentration of 30 mg/tablet gives the desired drug release rate from 15 mg/hr during a period of 6 h. **Table 5**. Further study with a higher concentration of sodium chloride in the core tablet resulted in the bursting of the tablet (40 mg NaCl). The 30 mg/tablet concentration of sodium chloride was selected as an optimized concentration of osmogen for further study.

TABLE 5: EFFECT OF SODIUM CHLORIDE ON DRUG RELEASE

Formulation Code	Drug Release (mg/h)
D1	8
D2	10
D3	12
D4	13
D5	15
D6	burst

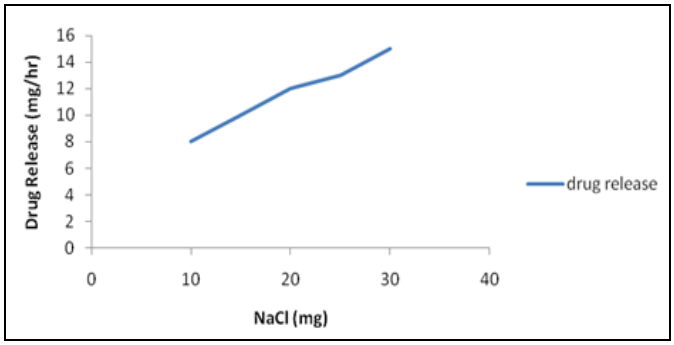

FIG. 1: EFFECT OF SODIUM CHLORIDE ON DRUG RELEASE

Precompression Studies: Many different properties have been employed to assess flowability, of these, angle of repose is the most relevant. The bulk density was found to be between 0.665 gm/cm^3. The value indicates a good packing capacity of powder. The tapped density of powder was found to be 0.759 gm/cm^3. The bulk density and tapped density was used to calculate the percent compressibility of the powder.

The value of Hausner's ratio was found to be 1.141, indicating good flowability. Carr's index of was observed 12.36%, indicating good compressibility of the powder.

Evaluation of Core Tablet: All formulated core tablets were shiny white with a smooth surface, circular curved faced with good texture. The thickness of the core tablet was found to be 5 mm, due to constant tablet press setting irrespective of weight variation.

The hardness of the tablet was found to be in the range of 6 to 7.0 kg/cm^2. This ensured good mechanical strength. The drug content of the tablet was found to be in the range of 99 to 101%.

Evaluation of Consistency of Coat: The consistency of coat was studied by using sodium chloride (30 mg) as an osmogen (excess of osmogen to burst the coat). It was observed that as the % weight gain increased, the consistency of coat increased, but the drug release decreased **Table 6**.

TABLE 6: EVALUATION OF CONSISTENCY OF COAT

Formulation code	Percentage Release	Coat Consistency
D1	105.19%	+
D2	98.09%	++
D3	85.65%	+++
D4	69.06%	+++
D5	65.91%	+++
D6	60.30%	+++

+: Burst, ++: Swell, +++: No change

Evaluation of Effect Different Concentration of Pore Former: Osmotic tablets were subjected to *in-vitro* drug release studies in the buffer of pH 7.5 for 8 hr, the dissolution profiles of all formulations were summarized in **Table 7**. Hence, it was evident that the increase in the concentration of pore former the drug release from the system was found to be increased.

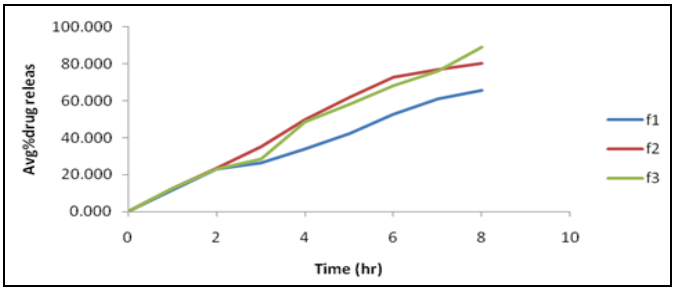

FIG. 2: EFFECT OF DIFFERENT CONCENTRATIONS OF SORBITOL ON DRUG RELEASE FROM CPOP

TABLE 7: DRUG RELEASE PROFILES OF F1 TO F4

Time (hrs)	Avg. % Drug Release			
	F1	F2	F3	F4
1	11.893	12.612	12.522	1.9
2	22.919	23.642	22.833	3.0
3	26.550	35.361	28.259	4.1
4	33.703	49.751	48.539	4.8
5	42.153	62.063	57.970	5.1
6	52.716	72.915	68.170	6.0
7	61.090	77.087	76.000	6.8
8	65.646	80.383	89.082	8.4

Kinetics of Drug Release: In the present study, the dissolution was analyzed by PCP Disso Version 2.08 software to study the kinetics of the drug release mechanism. The results showed that some of the formulations followed zero-order dissolution mode, and some followed the Peppas model. The R^2 value of all dissolution models was shown in **Table 8**. The value of n *i.e.* release exponent was found in the range of 0.81 to 0.96, which shoes release of drug from the system by anomalous transport.

TABLE 8: MODEL FITTING OF DIFFERENT FORMULATIONS

Formulation code	R^2					n	k
	Zero Order	First Order	Matrix	Peppas	Hixson Crowell		
F1	0.9927	0.9870	0.9525	0.9935	0.9934	0.8149	11.83
F2	0.9866	0.9864	0.9519	0.9956	0.9933	0.9360	12.79
F3	0.9963	0.9394	0.9920	0.9928	0.9735	0.9645	11.81
F4	0.9653	0.9691	0.9742	0.9922	0.9679	0.6517	1.959

TABLE 9: EFFECT OF pH ON DRUG RELEASE

Time (hr)	Average % drug release		
	Phosphate Buffer pH		
	4	6.8	7.5
1	12.971	12.701	12.522
2	22.206	23.103	22.833
3	27.899	28.442	28.259
4	48.266	48.722	48.539
5	58.055	58.423	57.970
6	68.436	68.536	68.170
7	75.728	75.829	76.000
8	88. 91	88.95	89.08

*All reading taken in trip

Effect of pH on Drug Release: To study the effect of pH, optimized formulation (F3) was subjected to dissolution studies separately in Phosphate buffer of pH 4 and Phosphate buffer of pH 6.8 for 8 h as given in **Table 9**. The system was independent of the pH, as there was no considerable difference in the drug release.

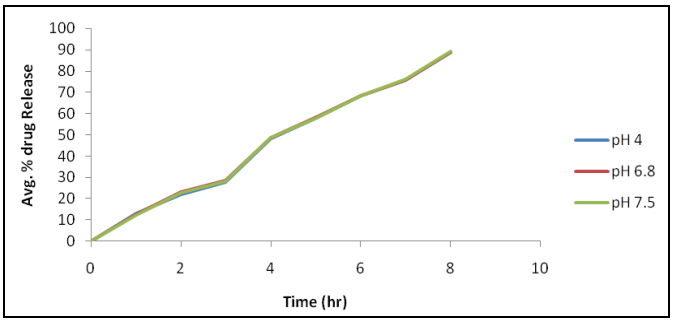

FIG. 3: EFFECT OF DIFFERENT PH ON RELEASE OF DRUG

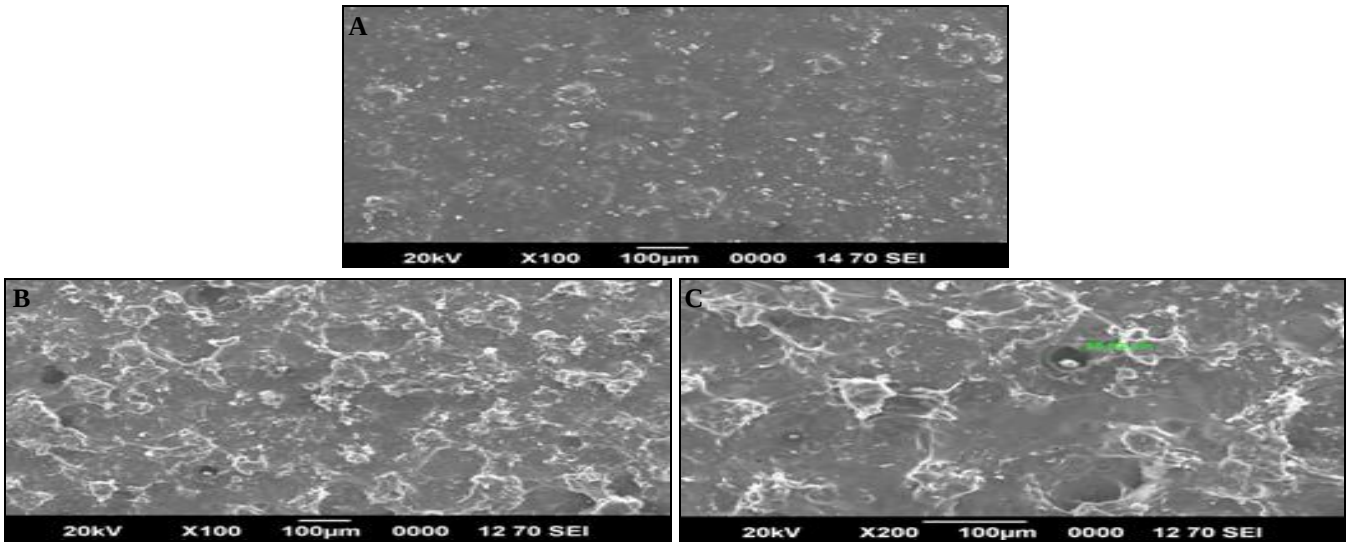

FIG. 4: (A) SEM MICROPHOTOGRAPH (AT 100X MAGNIFICATION) OF VERAPAMIL HCl CPOP TABLET BEFORE DISSOLUTION. (B) SEM MICROPHOTOGRAPH (AT 100X MAGNIFICATION) OF VERAPAMIL HCl CPOP TABLET AFTER DISSOLUTION. (C) SEM MICROPHOTOGRAPH (AT 200X MAGNIFICATION) OF VERAPAMIL HCl CPOP TABLET AFTER DISSOLUTION SHOWING PORE SIZE

Surface Morphology Study: To investigate the change in the membrane structure, surface of coated tablets (both before and after dissolution studies) was studied using Scanning Electron microscopy microphotographs showed in **Fig. 4 (a, b, c)** shows membrane structure before dissolution, initially, the surface of coated tablets was smooth before coming into contact with aqueous environment and coats appeared to be free of pores. A microporous structure of the membrane after dissolution was observed from **Fig. 4b**, which shows SEM of the membrane after dissolution. This significant porosity has resulted due to leaching of water-soluble additive *i.e.*, sorbitol during dissolution through which drug release takes place. **Fig. 4c** shows the pore size.

Stability Study: The optimized formulation F3 was subjected to the accelerated stability study at 40 ± 2 °C and 75 ± 5% RH for 3 months as per ICH guidelines. Drug release profile and visual appearance like dimension, color change, thickness were monitored for 3 months. The results of the accelerated stability studies revealed no significant change in the parameters. From **Table 10**, the considerable drug loss was not fond for 3 months. Therefore, the formulation of F3 is considered to be stable.

TABLE 10: STABILITY STUDY

Tests	Limits	Initial	1 Month	2 Months	3 Months
Appearance	No change	No change	No change	No change	No change
Assay	Verapamil hydrochloride USP (NLT 90% to NMT 110% of the labeled amount of Verapamil hydrochloride)	101.60	101.52	101.44	100.40
Cumulative Release (%)	1hr =2 to 12	12.94	12.80	12.65	12.47
	2hr =10 to 25	22.29	22.10	21.95	21.73
	4hr =25 to 50	48.65	48.61	48.45	48.21
	8hr= NLT 80	89.12	89.10	89.05	89.01

Comparative Study of CPOP and EOP: From the dissolution profile of EOP system **Table 11**, it was found that formulation F8 having an orifice size 0.5 mm delivered drug up to 7 h and formulation F9 (0.8 mm orifice size) for 6 h.

TABLE 11: COMPARATIVE STUDY OF CPOP AND EOP

Time (h)	Cumulative Drug Release (%)		
	F8	F9	F10
1	11.627	20.462	29.950
2	20.80	34.245	74.212
3	53.170	69.189	92.166
4	62.556	87.108	95.44
5	75.025	97.195	100.07
6	89.783	100.320	100.13
7	100.01	100.320	100.26
8	100.04	100.320	100.26

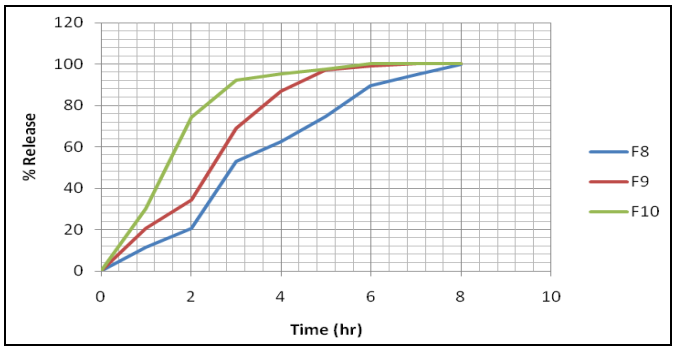

FIG. 5: DISSOLUTION PROFILE OF EOP TABLETS (F8 TO F10)

Formulation F10 with orifice size 1 mm released 100% drug within 5 h **Fig. 5**.

The study revealed that CPOP is superior to conventional EOP, because CPOP delivered Verapamil HCl for 8 h and also easier and cost-effective to formulate.

Comparative Study of CPOP and Marketed Sustained Release Tablet: From dissolution studies **Table 12**, it was revealed that the marketed Verapamil HCl SR formulation does not follow zero-order drug release pattern as that of CPOP.

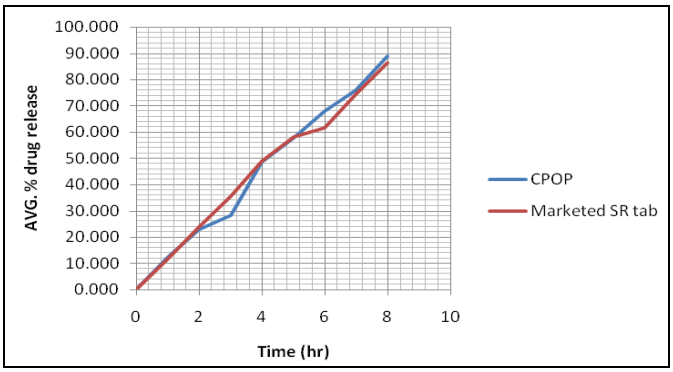

FIG. 6: COMPARATIVE DISSOLUTION PROFILE OF CPOP AND MARKETED SR TABLET

TABLE 12: COMPARATIVE DISSOLUTION PROFILE OF CPOP AND SR MARKETED TABLET

Time h	CPOP	Marketed SR formulation
1	12.522	11.803
2	22.833	23.817
3	28.259	35.448
4	48.539	48.849
5	57.970	58.192
6	68.170	61.476
7	76.000	74.300
8	89.082	86.384

CONCLUSION: The investigation carried out so far has encouraged for drawing the following conclusions:

- The release of Verapamil HCl was modulated through the incorporation of an optimized concentration of sodium chloride into the core tablet.
- The desired release of Verapamil HCl from the CPOP was achieved through careful monitoring of the selected formulation variables.
- Further, the release from the CPOP studies suggested that the desired consistency of the system could be considered while maintaining the desired release properties of the formulation.
- The effect of different pore former in three different concentrations evaluated in the study, which reveals that the sorbitol in the concentration of 25% w/w gives good and desired release as per USP acceptance criteria. It was evident that the increase in the concentration of pore former the drug release from the system was found to be increased.
- From the studies, it was revealed that the F3 is an optimized formulation that was used for further studies and evaluation.
- The optimized formulation (F3) delivered Verapamil HCl independent of pH and was found to be stable.

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CONFLICTS OF INTEREST: Nil

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