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Study and Optimization of Effect of Critical Formulation Components in The Manufacture of Multiparticulate Oral Controlled Release Drug Delivery System

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ABSTRACT
In recent years, there are so many controlled oral drug delivery system in that one of the advanced technique is pelletization. Propranolol hydrochloride which is an antihypertensive drug was formulated in the form of multiparticulate system. Wurster process was used in which pellets were designed with different material of construction of core pellets, binders and plasticizerpolymer ratio. The propranolol hydrochloride pellets were composed of water insoluble ethyl cellulose and water soluble hydroxyl propylmethyl cellulose polymer with PEG400 as a plasticizer for extended release action. The objective of the study was to identify the effect of critical variables related to formulation components on the release profile of extended release pellets so as to deliver a constant, predetermined amount of drug over 24 hr. Prepared pellets were evaluated for micromeritic properties, content uniformity and In-vitro drug release study. Dissolution studies revealed that the formulations containing sugar pellets showed faster release than microcrystalline cellulose pellets and MCC pellets (150-200µm) showed greater release than sugar pellets (500-600µm) and MCC pellets (300-500µm). PEG400- HPMC ratio of 2:1 and 3:1 showed slower release as compared with 1:1. Drug release decreased on increasing polymeric weight gain. There were not much difference found in release when HPMC (5cps), PVPk30 and PVPk90 used as a binder. Ethyl cellulose of 50cps retarded the release of drug as compared with 10cps. Therefore MCC pellets (150-200µm), HPMC as a binder, ethyl cellulose(10cps) and 1:1 ratio of PEG400 and HPMC were considered as an optimized components.
Keywords*: Pellets, Wursters process, Extended release polymers, Plasticizer, In-vitro dissolution studies.*

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INTRODUCTION

Sustained release products have acquired extraordinary attention in recent years. Sustained (or continuous) release of a drug involves polymers that release drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all advantages of a single unit formulations. Multiparticulates can be represented as novel drug delivery system in the form of intestinal protective drug absorption system (IPDAS), Spheroidal oral drug absorption systems (SODAS), Programmable oral drug absorption system (PRODAS), Diffucaps, Minitabs, Pelletised tablet, Multiparticulate drug dispersing shuttle, Macrocap, Orbexa, Flashtab, InnoHerb.[1] There are some approaches to multiparticulate formulation such as Floating- pulsatile delivery system, colonic delivery and mucoadhesive delivery system.These systems could facilely separate into sustained release units throughout the GIT after ingestion. One of the multiple unit dosage form is the pellets, which reduces variations in gastric emptying time and transit time, is less prone to dose dumping, and provides less irritation from high local absorption of drug.2The multiple unit dosage forms are preparations that consist of several mini reservoirs. Pellets are spherical agglomerated powders range in the size between 0.5 to 1.5mm, depending on the processing technique having narrow size distribution.[2] Pelletization techniques widely used in pharmaceutical industries are direct pelletization, extrusion spheronization and layering.The fluid bed process often is used for coating and powdered layering (pelletizing) applications. The bottom spray (wurster) fluid bed method is very

popular in the pharmaceutical industry for active layering and for coating to control drug release because it produces a superior film compared with other coating techniques.[3]
Propranolol hydrochloride was used as a model drug. Propranolol hydrochloride is a sympatholytic non selective beta blocker. It is about 90% bound to plasma protein; bioavailabilty is 26% and half-life is 4-5 hrs.[4]Hydrophillic polymer alone for controlling the drug release of highly water soluble drugs is bound to rapid diffusion of the dissolved drug through the hydrophilic gel layer. Use of hydrophobic polymers will retard the drug release. Plasticizers greatly affects the drug release because it improves the film forming properties and improves mechanical properties of polymer by reducing the GTT and increasing the plasticity or fluidity of the polymer. It dominate migration rate of drug.Hence the major aim of this work was to manufacture extended release pellets by using bottom spray method (wurster process) and evaluate how drug release from coated pellets is affected by changes in material of constructions of core pellets, for drug layering, types of binder used and for polymer coating, various formulation parameters were taken into consideration such as- higher grades of ethyl cellulose polymer, plasticizer & polymer ratio and % weight gain of polymer coating.[5-6]

MATERIAL AND METHODS

Materials: Propranol hydrochloride(IPCA Laboratories Ltd. Mumbai), Sugar pellets of 500-600µm (Werner, Germany), Microcrystalline cellulose (MCC)pellets of 150-200µm and MCC pellets of 300-500µm (Asahi Kasei Chemical Corporation), PVPk30, PVPk90 and PEG400 (BASF, Mumbai), Talc of USP grade (Emcure Pharmaceuticals Limited, Pune), Ethyl cellulose (EC) of 10 & 50 cps and Hydroxypropyl methyl cellulose (HPMC) of 5 cps (Colorcon Asia Private Limited, Goa), Isopropyl alcohol (IPA), Dichloromethane (DCM) and Methanol (Merck Specialities Private Limited, Mumbai) were used as formulation components. All chemical reagents were of analytical grade and used without any further purification. Only compatible excipients were used based on literature survey.

Experimental work

Preparation of drug layered pellets:

Preparation of drug solution: The drug solution was prepared by adding HPMC 5 cps in a solvent mixture of purified water & methanol (20:80) with continuous stirring using a mechanical stirrer until to form clear solution. To that solution propranolol hydrochloride (PHCL) was added with continuous stirring for about 20 minutes until to form clear solution.

Drug layering: Fluidized bed processor (bottom spray method), Umang PharmatechPvt. Ltd, was used for coating of PHCL over the MCC pellets. 300gm of MCC pellets of 150-200µm were weighed and loaded into the wurster chamber, fluidized anddrug solution was sprayed onto MCC pellets with following parameter given in table 1. The composition of core pellets were given in table 4.[7]

Table No. 1: Process parameters for drug layering

Sr.No.	Parameters		Description
1	Inlet Temperature		47-53°C
2	Product Temperature		30-35°C
3	Spray rate		1.6-4.0 g per min
4	Air flow (Atomization)		1.5 bar
5	Blower RPM		1300-1750
7	Wurster Column	For 40 L	Height- 1.5-2 cm
8	Sieve size		200 micron
9	Nozzle	For 40 L	0.2 mm

Preparation of extended release pellets:

Preparation of polymer coating solution: Polymer coating solution was prepared by initially dry mixing of 62.5% Ethyl Cellulose (10cps), 17.5% HPMC (5cps) &2.5% Talc. This dry mixture was added to the solvent of Isopropyl alcohol in which 17.5% PEG400 was added as a plasticizer (1:1 ratio of PEG400 and HPMC were used)with continuous stirring using a mechanical stirrer until to form viscous solution. To that solution dichloromethane was added slowly to avoid the lumps formation with continuous stirring until to form viscous solution.

Polymer coating:350gm drug layered pellets containing 160mg drug per 239.9mg of pellets were coated to yield a 35 % increase in weight. Percentage weight gain was calculated by following equation:

$$\text{Percentage weight gain} = \frac{[(Wt - Wo)]}{W_o} \times 100$$

Where Wt = Weight of tablet after coating and Wo= Initial weight of tablet
The drug layered pellets were loaded into the wurster chamber, fluidized and polymer solution was sprayed on that with following parameter given in table 2. The composition for polymer coating onto the drug layered pellets is given in table 5 [8-9].

Table No. 2: Process parameters for extended release coatings

Sr.No.	Parameters	Description
1	Inlet Temperature	47-51°C
2	Product Temperature	30-35°C
3	Spray rate	1.5-3.0 g per min
4	Air flow (Atomization)	1.5-2 bar
5	Blower RPM (fluidization)	1200-1400

Composition variable study: An optimized batch was studied further for formulation variables to see the effect of excipient variables on consistency of drug release from pellets containing capsules as given in table 3 and formulation design for drug layered pellets and polymer coated pellets are given in table 4 and 5 respectively.

Table No. 3: Composition variables for manufacturing of extended release pellets

Sr. No.	Formulation Variables	
1	Material of construction of Core Pellet	(i) Sugar Spheres(F1) (ii) MCCSpheres(300-500micron)(F2)
2	Types of Binder (Drug Loading)	(i) PVPk30(F3) (ii) PVPk90(F4)
3 Polymer Variables		
	(a) PEG400: HPMC ratio	(i) 2:1(F5) (ii) 3:1(F6)
	(b) Ethyl Cellulose grades	(i) 50cps(F7)
	(c) Coating Variables(% wt.gain)	19%, 30%,40% (F8)

Table No. 4: Formulation design of drug layered pellets

Sr. No.	Ingredients	Optimized composition	F1	F2	F3	F4
1	Propranolol hydrocholride	160mg	160mg	160mg	160mg	160mg
2	Sugar pellets	-	71.9mg	-	-	-
3	MCC pellets (150-200µm)	71.9mg	-	-	71.9mg	71.9mg
4	MCC pellets (300-500µm)	-	-	71.9mg	-	-
5	HPMC (5cps)	8.0mg	8.0mg	8.0mg	-	-
6	PVPk30	-	-	-	8.0mg	-
7	PVPk90	-	-	-	-	8.0mg
8	Methanol	561.85mg	561.85mg	561.85mg	561.85mg	561.85mg
9	Purified water	140.50mg	140.50mg	140.50mg	140.50mg	140.50mg
10	**Total**	**239.9mg**	**239.9mg**	**239.9mg**	**239.9mg**	**239.9mg**

Table No. 5: Formulation design of extended release coating

Sr. No.	Ingredients	Optimize formula	F1	F2	F3	F4	F5	F6	F7	$F8_1$	$F8_2$	$F8_3$
										19%	**30%**	**40%**
1	Drug loaded pellets	239.9	239.9	239.9	239.9	239.9	239.9	239.9	239.9	239.9	239.9	239.9
2	Ethyl cellulose (10cps)	52.48	52.48	52.48	52.48	52.48	52.48	52.48	-	28.02	44.98	59.97
3	Ethyl cellulose (50cps)	-	-	-	-	-	-	-	52.48	-	44.98	59.97
4	HPMC(5cps)	14.69	14.69	14.69	14.69	14.69	9.79	7.34	14.69	7.84	12.59	16.79
5	PEG400	14.69	14.69	14.69	14.69	14.69	19.59	22.04	14.69	7.84	12.59	16.79
6	Talc	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	1.12	1.8	2.4
7	Isopropyl Alcohol	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
8	Dichloro methane	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
	Total(mg)	323.86	323.86	323.86	323.86	323.86	323.86	323.86	323.86	284.72	311.86	335.85

Evaluation methods:

Physical characterization of polymer coated pellets:

Particle size distribution (sieve analysis): The pellets were characterized for the size and shape. The formula through which mean diameter of the pellets can be calculated is given below,

Mean diameter = [Σ (% retained) x (mean aperture)] / 100

Where, mean aperture is taken as that mesh size at which pellets shows maximum retention &

Σ (% retained) = summation of % retained on each sieve.

20 gm of extended release pellets were sieved through 20, 25, 30, 35, 40 and the percentage weight distribution was determined.

Bulk density and Tapped density:

Apparent bulk density and tapped density were determined by placing pellets into graduated cylinder and measuring the volume and weight "as it is" and after tapping respectively. The Carr's compressibility index and hausner's ratio were also computed.

Friability:

Friability studies on core pellets were performed by placing 5g in a friabilator (Veego, Mumbai) and tumbled for 200 revolutions at 25rpm. Twelve steel balls (diameter 6.3mm, weighing 1.028g each) were used as attrition agents. The weight loss (%F) after friability testing was calculated.

Drug content uniformity:

100mg pellets were dissolved in 100ml distilled water. The resulting solution was suitably diluted and analysed on UV spectrophotometer Shimadzu at 320nm.

***In-vitro* release testing:**

The dissolution test of propranolol hydrochloride was performed by using dissolution test apparatus type I in 900ml of pH 1.2 buffer solution for 1.5 hr and in 900ml of pH 6.8 buffer solution conducted for 2.5 hr and for additional time points of 4, 14 and 24 hr at 100 RPM. 10ml aliquots were withdrawn with the pipette and replaced with 10 ml fresh buffer at different time intervals. The absorbance of sample were taken on UV spectrophotometer at 320nm and correspondingly concentration of drug was determined at various time intervals.[10]

RESULTS AND DISCUSSION

The system consisting of drug containing core pellets prepared by fluid bed coating process. The drug loaded core pellets were prepared by using binder and MCC core pellets. HPMC incorporates binding properties to pellets for sufficient hardness to withstand mechanical tension in coating pan. Further, the drug loaded core pellets were coated with combination of ethyl cellulose and different ratios of hydroxypropyl methyl cellulose and PEG400 as a plasticizer. Talc was used as an antitacking agent to prevent formation of agglomerates among the pellets.

Pellets characterization:

It was observed that the pellets were uniform in size and shape. The uniform size of pellets indicates good content uniformity, good flow and ease of capsule filling.

Friability:

Friability of the pellets is an important parameter to withstand handling, shipping and storage and other processing parameters such as coating. The weight loss (%F) after friability testing for all the formulations were calculated as 0.39 to 0.79 showing good friability.

Micromeritic properties:

The micromeritic properties of polymer coated pellets are depicted in table 6. The car's index and hausner's ratio for all formulations were found to be excellent.

Table No.6: Evaluation of polymer coated pellets

Parameters	Polymer coated pellets										
	Optimized composition	F1	F2	F3	F4	F5	F6	F7	$F8_1$	$F8_2$	$F8_3$
									19%	30%	40%
Angle of repose (degree)	20.92	14	15	19	17.6	14.19	18.26	20.81	20	16.7	15.2
Bulk density (gm/cc)	0.75	0.66	0.80	0.74	0.75	0.77	0.71	0.71	0.69	0.74	0.74
Tapped density (gm/cc)	0.78	0.74	0.83	0.76	0.79	0.80	0.77	0.77	0.78	0.79	0.76
Carr's index (%)	7.85	10	4.00	7.79	7.84	3.85	7.14	7.14	9.89	7.34	7.42
Hausner's ratio	1.09	1.11	1.04	1.05	1.06	1.04	1.07	1.07	1.17	1.01	1.02

Drug content:
The drug content uniformity was performed for drug loaded pellets. Three trials from each formulations were analyzed spectrophotometrically. The average values were also calculated. The percentage drug content were found to be 98% for the core pellets indicating good content uniformity. This indicates that drug was uniformly distributed throughout the core pellets.

***In-vitro* drug release study:**
In order to assess the effect of combination of hydrophilic and hydrophobic polymer, *In- vitro* dissolution studies were performed for the pellets which is shown in a table 7 and graphical representation of different formulations are given in Fig 1, 2, 3, 4 and 5.

Table No. 7: In-vitro release of pellets of different formulations

Time(hrs)	Percentage amount of drug released										
	Optimized composition	F1	F2	F3	F4	F5	F6	F7	$F8_1$	$F8_2$	$F8_3$
1.5	5.99	1.72	5.62	12.80	12.65	13.48	7.68	2.16	12.70	16.21	9.90
4	49.38	12.31	20.5	42.52	40.31	29.89	18.84	19.04	41.52	49.70	30.51
8	69.40	31.18	41.78	70.94	69.47	49.07	31.32	49.65	69.57	74.56	61.72
14	79.70	48.83	47.82	79.12	77.42	66.16	41.88	61.15	76.43	81.49	73.98
24	93.90	67.86	53.44	87.36	85.21	78.97	62.74	82.20	85.41	101.73	79.62

Core pellet variable study (F1 & F2):
MCC pellets of size 300-500µm and sugar pellets of size 500-600µm were taken. MCC pellets (300-500µm) showed much less release as compared with sugar pellets. This phenomenon attributes to hydrophilic and insoluble nature of MCC and soluble nature of sugar pellets. This could be beneficial to the dissolution of drugs with poor solubility. The strong osmotic activity of sucrose starter cores has also been suggested to cause faster and higher water uptake. At initial, MCC spheres showed burst release effect due to its hydrophilic nature [11, 12]. Sugar pellets and MCC (300-500µm) showed much less release profile as compared with MCC (150-200µm). The reason is MCC pellets (200-300µm) have smaller particle size than sugar pellets and MCC pellets (300-500µm). Due to its smaller pt. size, surface area of the particle was more which showed more absorption on drug release from the pellets. Dissolution graph is shown in Fig 1.[11]

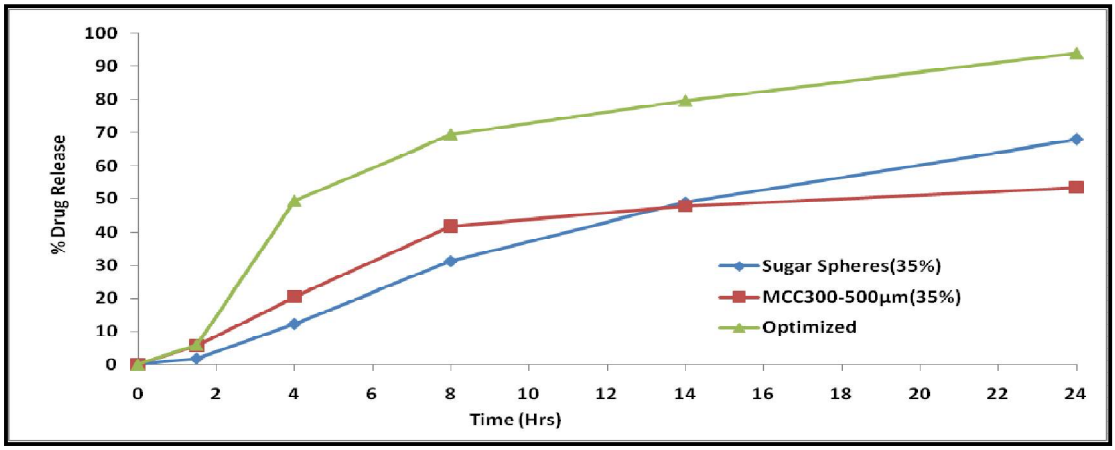

Figure 1: Dissolution graph of optimized composition and formulations containing Sugar pellets (500-600µm) and MCC pellets (300-500µm) (F1 & F2).

Binder variables study (F3 & F4):
The molecular weight and viscosity of povidone is the function of its k-value which means that molecular weight and viscosity of povidone increases on increasing the k-value of povidone. The drug release in case of PVPk90 is slightly slower than in case of PVPK30. This is due to high viscous nature of K90 as compared to K30 which shows high binding effect of an active drug on the base pellets. This results in retardation of drug release from the base core pellets. The hydration of the polymer produces highly viscous gel that plays an important role in release of drug, especially at the beginning of the release profile as shown in Fig 2.[12]

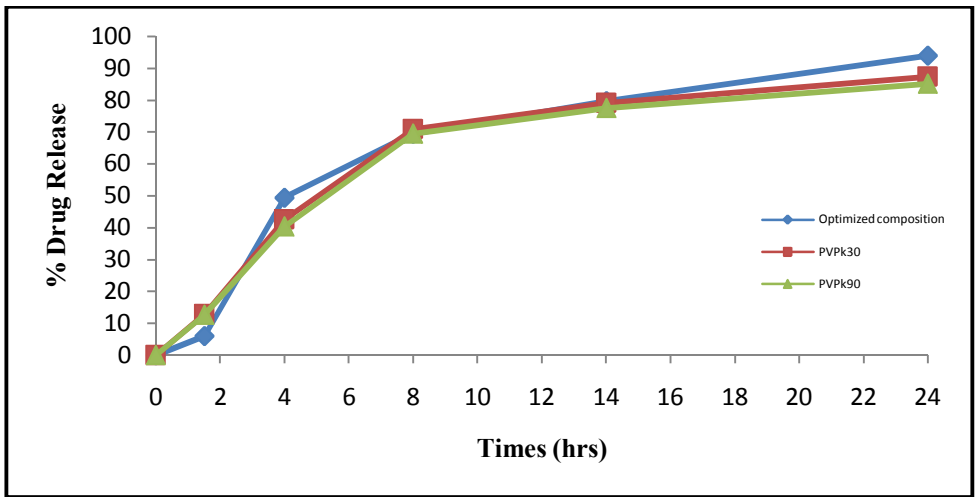

Figure 2:Dissolution graph of optimized composition and formulations containing PVPk30 and PVPk90 as a binder (F3 & F4).

Plasticizer –Polymer ratio variables study

Release of the drug was decreasing from the pellets on increasing the amount of PEG400 as compared with an optimized concentration ratio (1:1). This may be due to dominating effect of ethyl cellulose which acts as drug release rate retardant polymer and decrease in the amount of HPMC a water soluble polymer. An addition of a PEG400 plasticizer to the polymeric networks will increase the flexibility of coatings so that it can form a continuous film rather than brittle and porous film of ethyl cellulose polymer on the surface of drug loaded pellets. On the other hand HPMC swells when comes in contact with water due to its water swellable nature and forms pores on the polymeric film so that the drug could easily come out from the polymeric membrane. As the amount of HPMC decreases it forms less porous structure of polymeric film and retard drug release. PEG400 was found to enhance water vapour permeability of HPMC free films which leads to increase in the mobility of polymeric molecules of HPMC. This is the reason that inclusion of increased amount of PEG400 with respect to decreased amount of HPMC resulted in the production of a smoother, more homogeneous film with less cracks. Dissolution graph were shown in Fig 3.

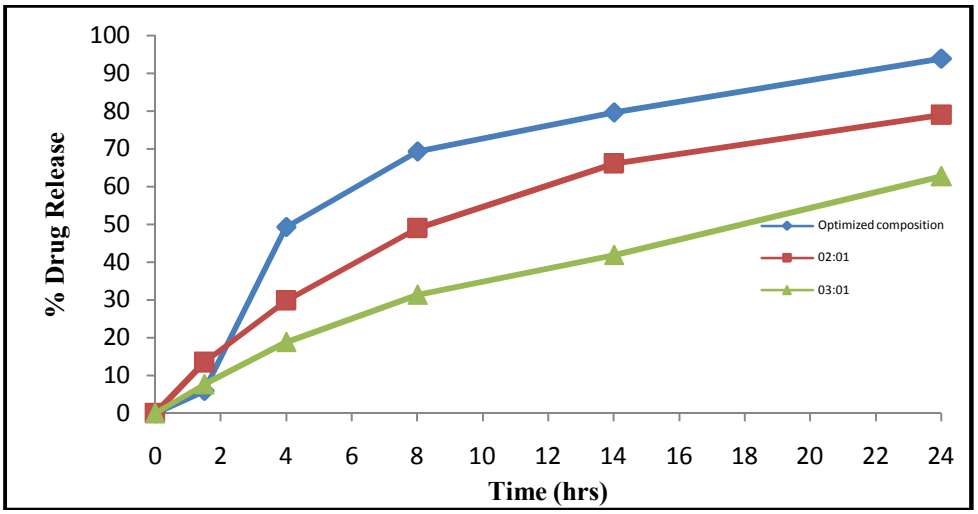

Figure 3: Dissolution graph of optimized composition formulations containing PEG400 and HPMC (5cps) of ratio 2:1 and 3:1 (F5 & F6).

Polymer variables study (F7):

Polymer content was associated with a corresponding decrease in the drug release rate, hence drug release were found to be decrease with increase in the polymeric weight gain and drug release pattern was found to be much slower than the optimized composition because Ethyl cellulose of 50cps has greater viscosity than ethyl cellulose of grade 10cps due to higher content of ethoxyl group. Due to more

viscous nature of ethyl cellulose of 50cps, it forms more viscous and compact layer onto the surface of the pellets and readily retards release of drug were shown in Fig 4.[13]

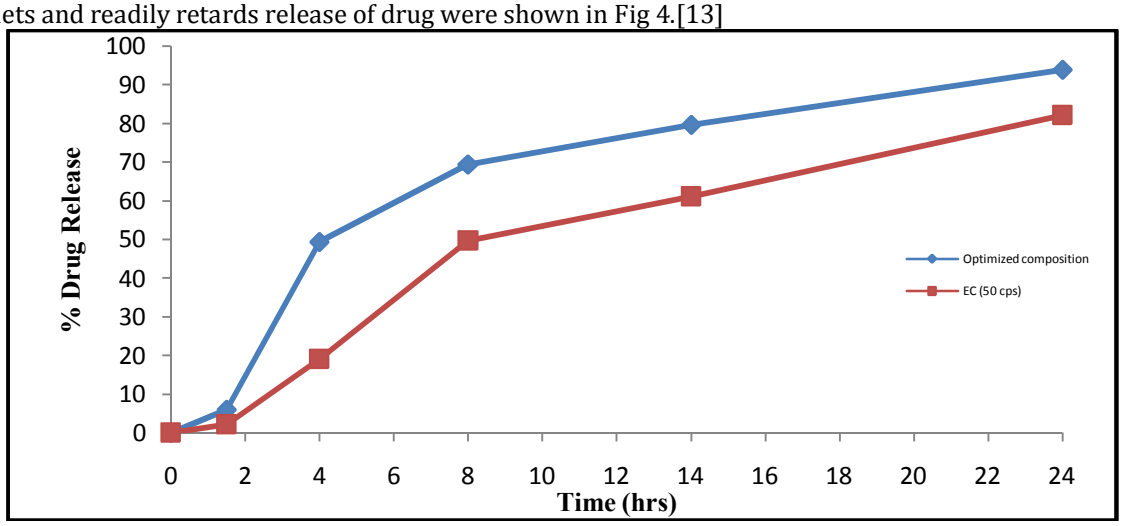

Figure 4: Dissolution graph of optimized composition and formulation containing Ethyl cellulose of 50cps(F7).

4.1.9 Coating variable study ($F8_1$, $F8_2$ $F8_3$):

19% wt. gain was taken in case of sugar pellets and 30%, 35% & 40% wt. gain were taken in case of MCC pellets. The above graph shows that drug release from the pellets decreases on increasing the polymer coating wt. on drug loaded pellets due to increased amount of ethyl cellulose and HPMC polymer content. However in case of 19% wt. gain of sugar pellets, drug release profile is somewhat similar to 35% wt. gain. This is because of increased particle size of core sugar pellets requires less polymer wt. gain to decrease surface area of the pellets so that the absorption of the drug could delay from the pellets through GI membrane. Dissolution graph were shown in Fig 5.[14]

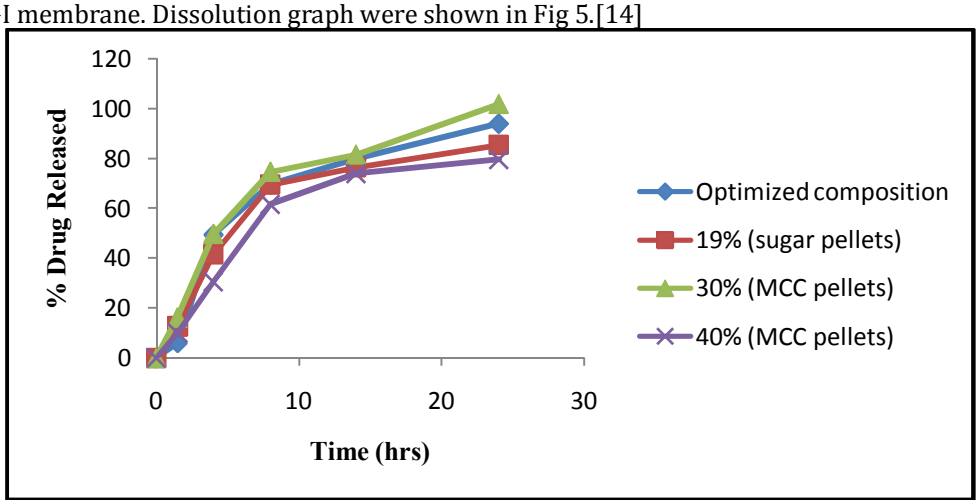

Figure 5: Dissolution graph of optimized composition and formulations containing Sugar pellets having 19% and MCC pellets having 30% and 40% polymer coating weight gain .

CONCLUSION

The material of construction had greater impact on drug release. Small particle size require more polymer coating in terms of weight gain to increase the particle size of the core pellets On increasing the viscosity grades of PVP, aqueous solubility of the polymer attributes to increase in viscous nature of the PVP which slowly dissolves the drug along with itself from the pellets. The addition of HPMC to ethyl cellulose barrier membrane coatings resulted in drug release over 24 hrs. Dissolution rate and extent of drug release decreased with increasing PEG400 and decreasing HPMC content. Concentration of plasticizers can affect the film properties, as revealed by several investigations (variable study). So according to the desired release profile, we can adjust the ratio of Plasticizer and polymer. Therefore, MCC Pellets, Ethyl Cellulose (10cps), PEG400 & HPMC of ratio 1:1 and 35% polymer coating weight gain were considered as optimized components to get the desired release profile of the pellets on the basis of USP specification limits.

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